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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**

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#### **Table of Contents**

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

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

**Table S3.** Associations of ln-transformed PFAS concentration with PCOS-related infertility in logistic regression model among nulliparous women (n = 792).

**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).

**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)

**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)

**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).

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

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

**Figure 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.

**Figure 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.

**Figure 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.

**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.

**Figure 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.

**Additional File-** Excel Document

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

PFAS <sup>a</sup>	group	All subjects <sup>a</sup> (n = 943)		Normal weight (n = 622)		Overweight or obese (n = 321)	
		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
∑3,4,5m-PFOS	2	<b>0.107</b>	<b>0.456</b>	0.016	0.089	<b>0.122</b>	<b>0.452</b>
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	<b>0.616</b>	<b>0.109</b>	0.045	0.042	<b>0.872</b>	<b>0.102</b>
PFUDA	1	0.616	0.007	0.045	0.015	0.872	0.014
6:2 Cl-PFESA	1	<b>0.616</b>	<b>0.642</b>	<b>0.045</b>	<b>0.656</b>	<b>0.872</b>	<b>0.695</b>
8:2 Cl-PFESA	1	0.616	0.006	0.045	0.049	0.872	0.002
HFPO-DA	1	<b>0.616</b>	<b>0.126</b>	<b>0.045</b>	<b>0.112</b>	<b>0.872</b>	<b>0.099</b>
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

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.

<sup>a</sup> For full chemical names see Table 1.

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

PFAS (ng/mL) <sup>a</sup>	PCOS (n=299)	Non-PCOS (n=531)	Adjusted OR <sup>b</sup> (95% CI)	P-value*
	Median (P25-P75)	Median (P25-P75)		
<i>Legacy PFAS</i>				
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)	<b>1.32 (1.20-1.51)</b>	<b>0.006</b>
PFUDA	0.66 (0.44-1.21)	0.51 (0.24-1.10)	1.07 (0.72-1.29)	0.50
<i>PFAS isomers</i>				
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)	<b>1.35 (1.09-1.67)</b>	<b>0.003</b>
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)	<b>1.15 (1.05-1.37)</b>	<b>0.02</b>
∑3,4,5m-PFOS	0.60 (0.38-1.11)	0.51 (0.26-0.96)	<b>1.31 (1.12-1.56)</b>	<b>0.0007</b>
<i>PFAS alternatives</i>				
6:2 Cl-PFESA	3.63 (2.52-6.39)	2.59 (1.18-6.06)	<b>1.21 (1.06-1.37)</b>	<b>0.0002</b>
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)	<b>1.39 (1.21-1.75)</b>	<b>0.001</b>
<i>Short-chain PFAS</i>				
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)	<b>0.85 (0.71-1.00)</b>	<b>0.05</b>
PFPeS	0.01 (0.01-0.01)	0.01 (0.00-0.01)	<b>1.16 (1.04-1.32)</b>	<b>0.04</b>
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)	<b>1.16 (1.05-1.31)</b>	<b>0.01</b>
PFHpA	0.07 (0.05-0.11)	0.05 (0.03-0.08)	1.09 (0.91-1.20)	0.18

Abbreviations: OR, odds ratio; CI, confidence interval; PCOS, polycystic ovarian syndrome.

Note: PBAC scoring  $\geq 100$  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.

<sup>a</sup> For full chemical names see Table 1.

<sup>b</sup> Adjusted for age (linear), BMI (categorical), annual household income (categorical), educational level (categorical), study site (categorical) and age at menarche (linear).

**Table S3.** Associations of ln-transformed PFAS concentration with PCOS-related infertility in logistic regression model among nulliparous women (n = 792).

PFAS <sup>a</sup>	PCOS (n=300)	Non-PCOS (n=492)	Adjusted OR <sup>b</sup> (95% CI)	<i>p</i> -value*
	Median (P25-P75)	Median (P25-P75)		
<i>Legacy PFAS</i>				
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)	<b>1.32 (1.18-1.56)</b>	<b>0.003</b>
PFUDA	0.64 (0.41-1.16)	0.51 (0.24-1.11)	1.24 (0.81-1.61)	0.56
<i>PFAS isomers</i>				
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)	<b>1.26 (1.08-1.46)</b>	<b>0.02</b>
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)	<b>1.25 (1.12-1.47)</b>	<b>0.01</b>
∑3,4,5m-PFOS	0.57 (0.38-1.11)	0.49 (0.26-0.96)	<b>1.29 (1.16-1.63)</b>	<b>0.0009</b>
<i>PFAS alternatives</i>				
6:2 Cl-PFESA	3.66 (2.49-6.00)	2.57 (1.16-6.00)	<b>1.31 (1.11-1.52)</b>	<b>0.0002</b>
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)	<b>1.23 (1.06-1.47)</b>	<b>0.003</b>
<i>Short-chain PFAS</i>				
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

PFFPeS	0.01 (0.01-0.01)	0.01 (0.00-0.01)	1.09 (0.97-1.26)	0.29
PFFPeA	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)	<b>1.21 (1.08-1.42)</b>	<b>0.02</b>
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.

<sup>a</sup> For full chemical names see Table 1.

<sup>b</sup> 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 <sup>a</sup> tertiles (ng/mL)	Adjusted OR <sup>b</sup> (95%CI)
6:2 CI-PFESA	
Q1 (<2.72)	Ref
Q2 (2.72-4.86)	<b>1.26 (1.08-1.56)</b>
Q3 (≥4.86)	<b>1.46 (1.15-1.79)</b>
8:2 CI-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)	<b>1.19 (1.07-1.41)</b>
Q3 (≥0.04)	<b>1.45 (1.19-1.71)</b>

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.

<sup>a</sup> For full chemical names see Table 1.

<sup>b</sup> 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 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).

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

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.

<sup>a</sup> For full chemical names see Table 1.

<sup>b</sup> 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 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).

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

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.

<sup>a</sup> For full chemical names see Table 1.

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



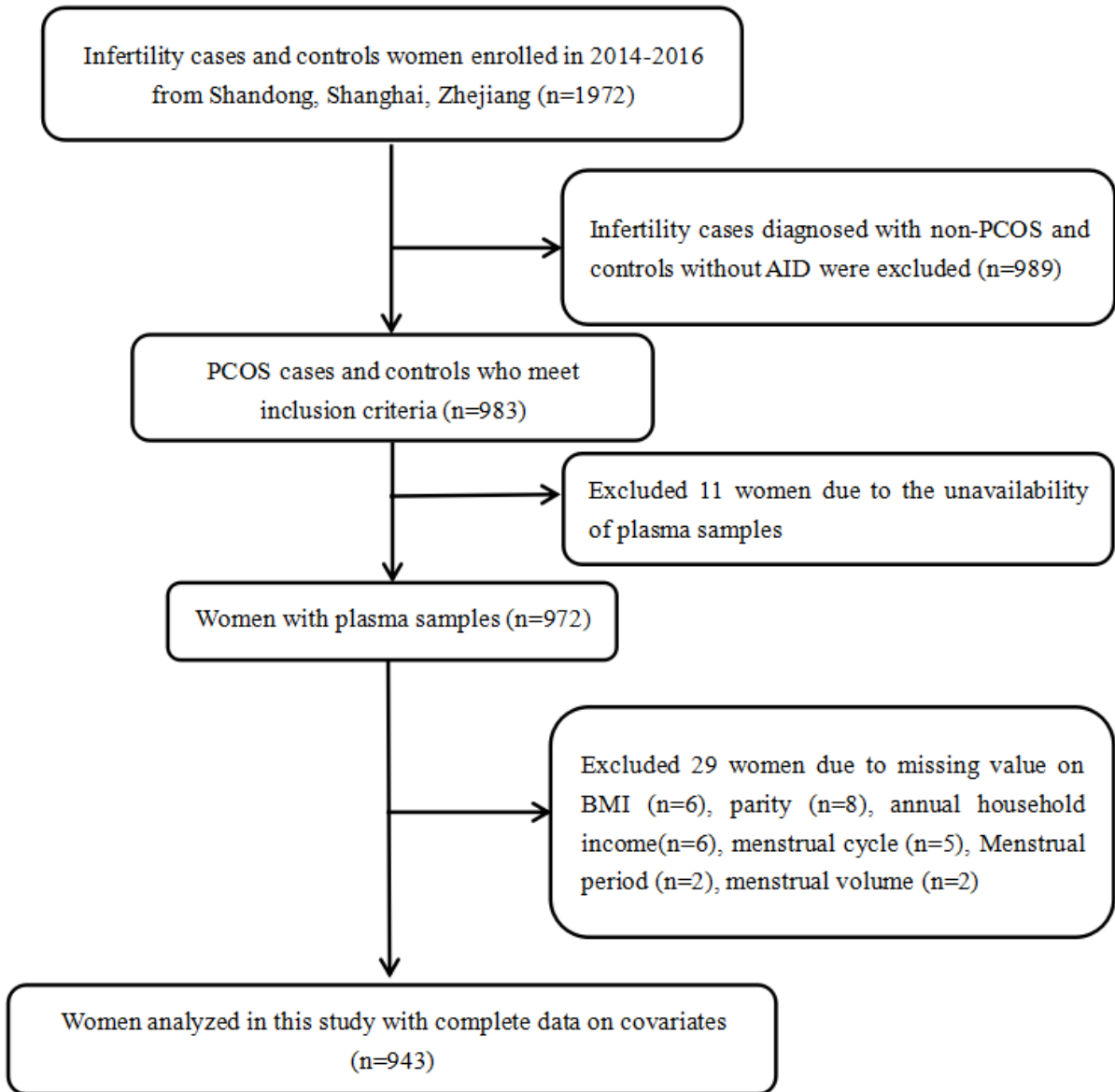
**Table S7.** Odds ratios (OR) and 95%CI confidence interval (CIs) for polycystic ovary syndrome (PCOS) in tertiles of short-chain PFAS in logistic regression model (n = 943).

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

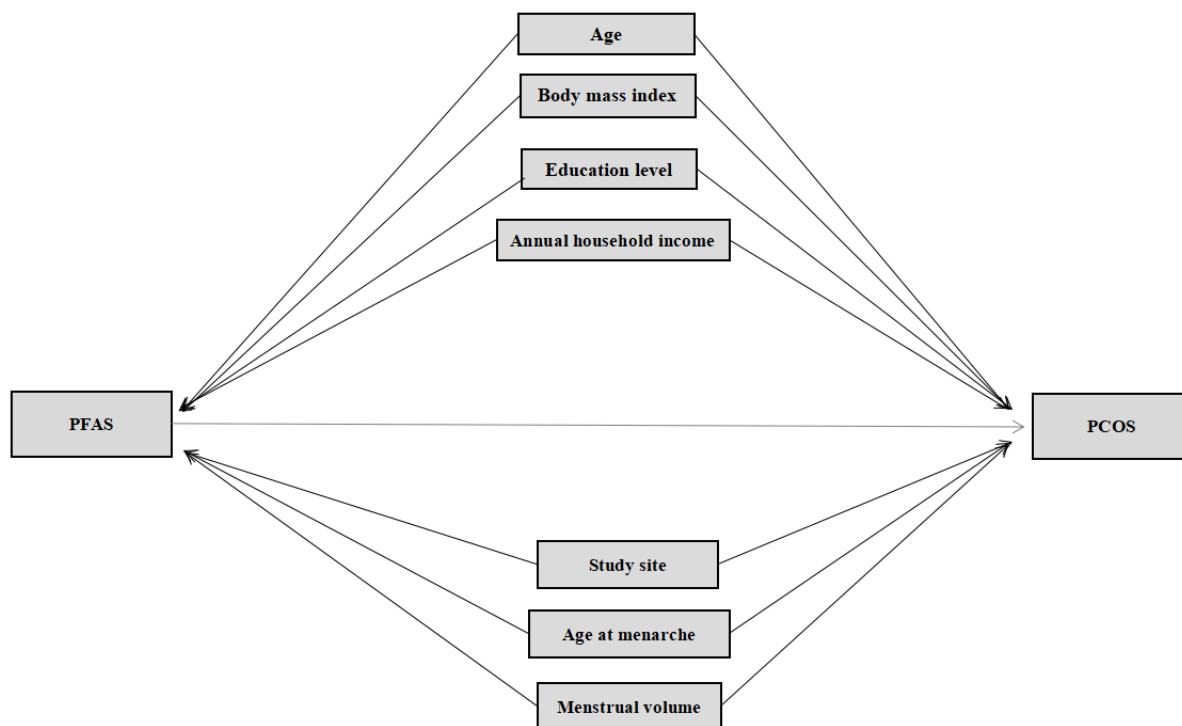
Note: The tertiles are defined as all participants were divided equally into three equal parts, with 314 (Q1), 315 (Q2) and 314 (Q3) participants in each of the three parts.

<sup>a</sup> For full chemical names see Table 1.

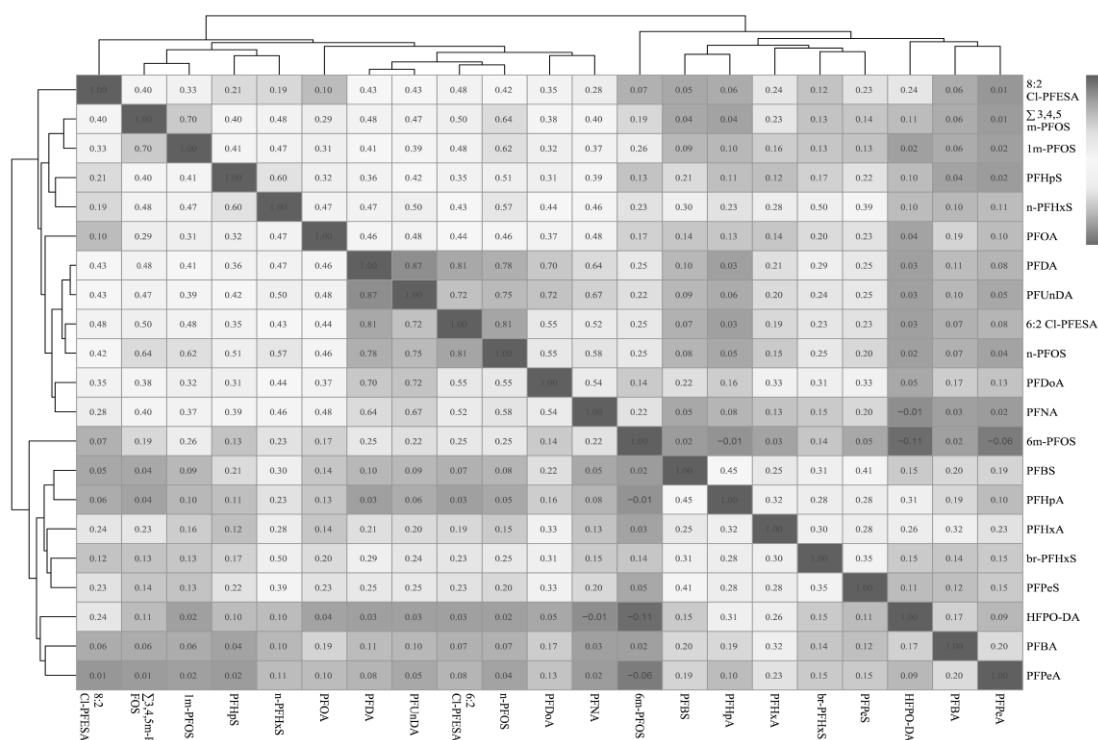
<sup>b</sup> Adjusted for age (linear), BMI (categorical), annual household income (categorical), educational level (categorical), study site (categorical), age at menarche (linear) and menstrual volume (categorical).



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

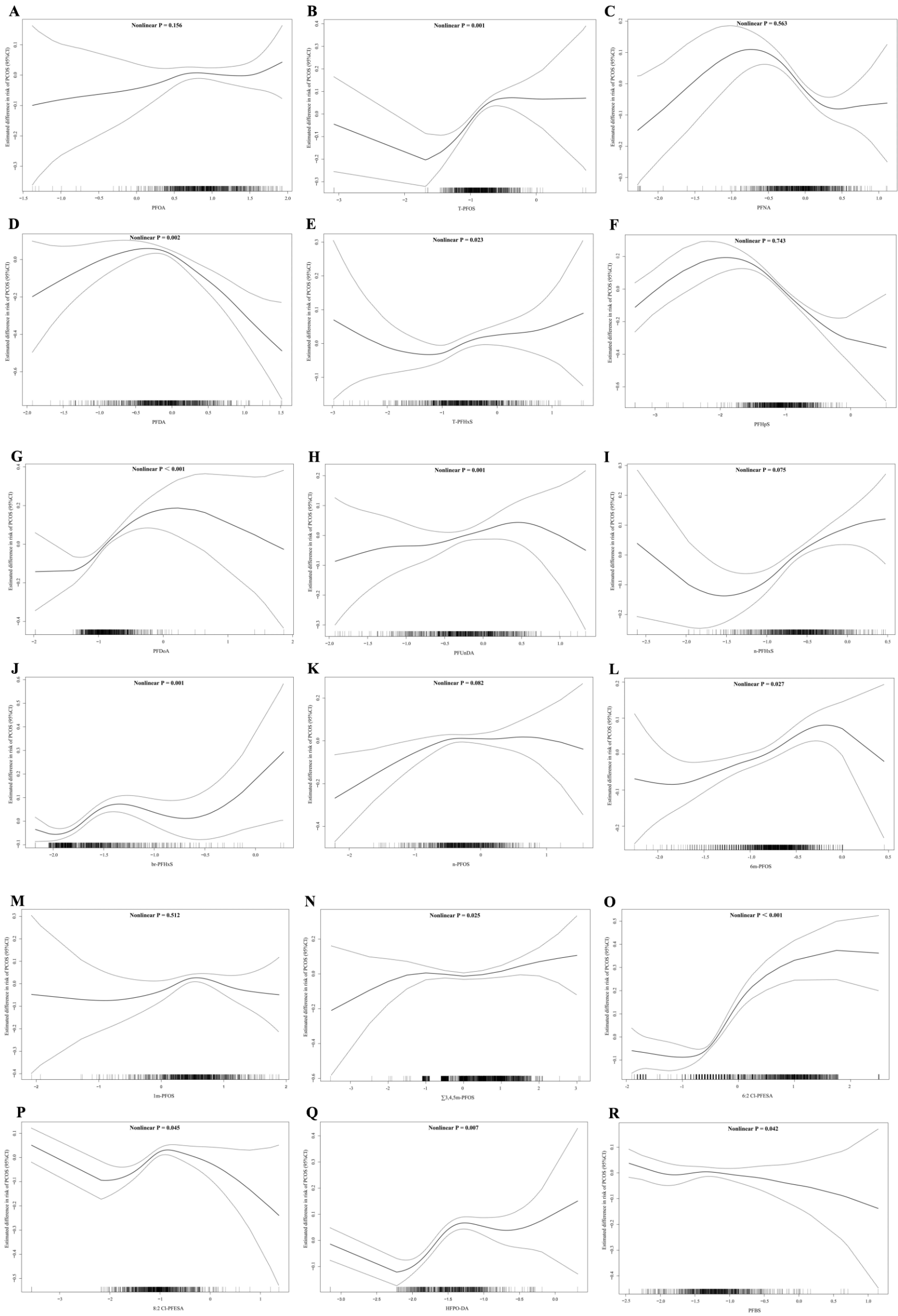


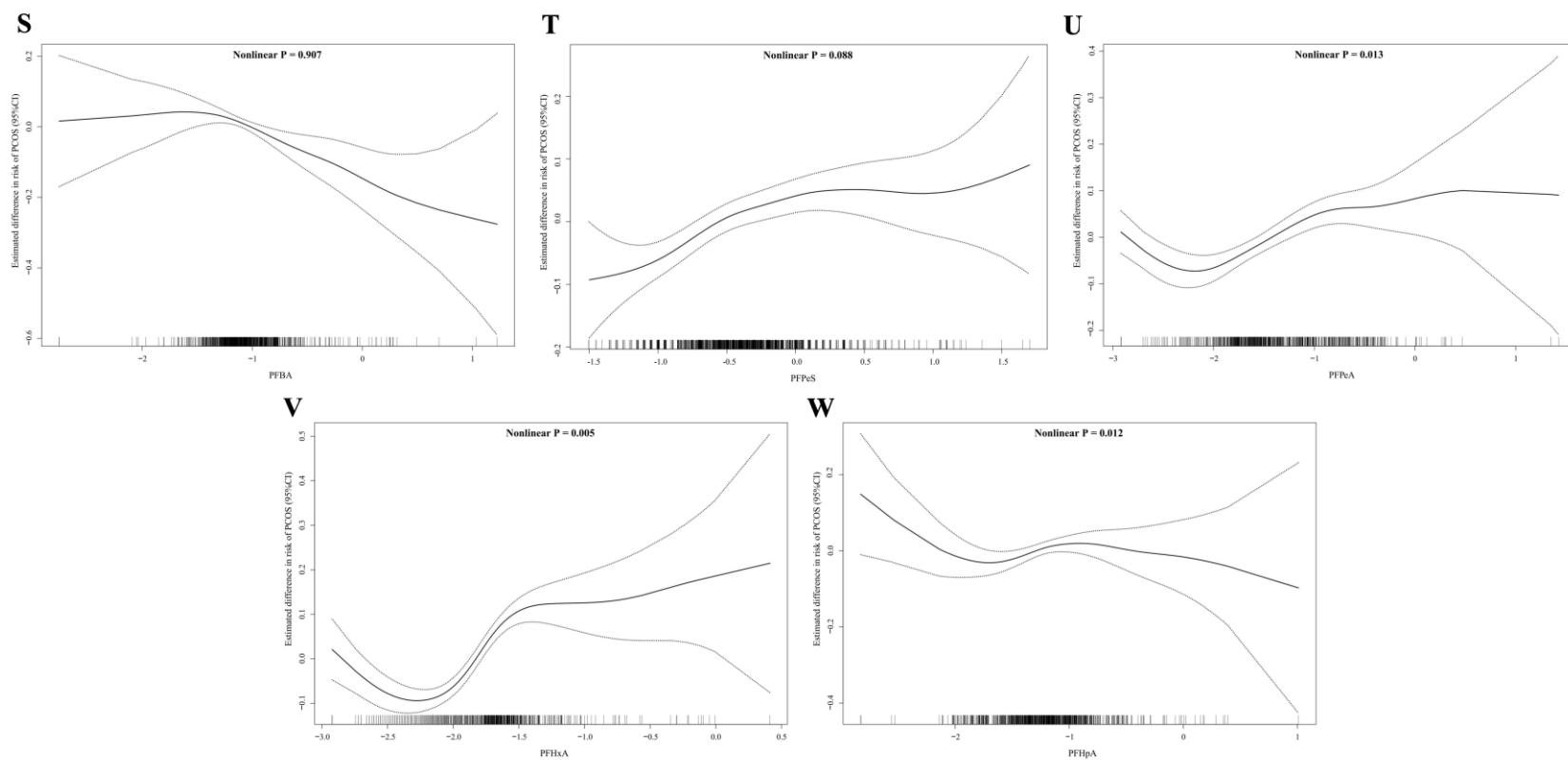
**Fig. S2.** Directed Acyclic Graph for covariate selection. Abbreviations: PCOS, polycystic ovarian syndrome.



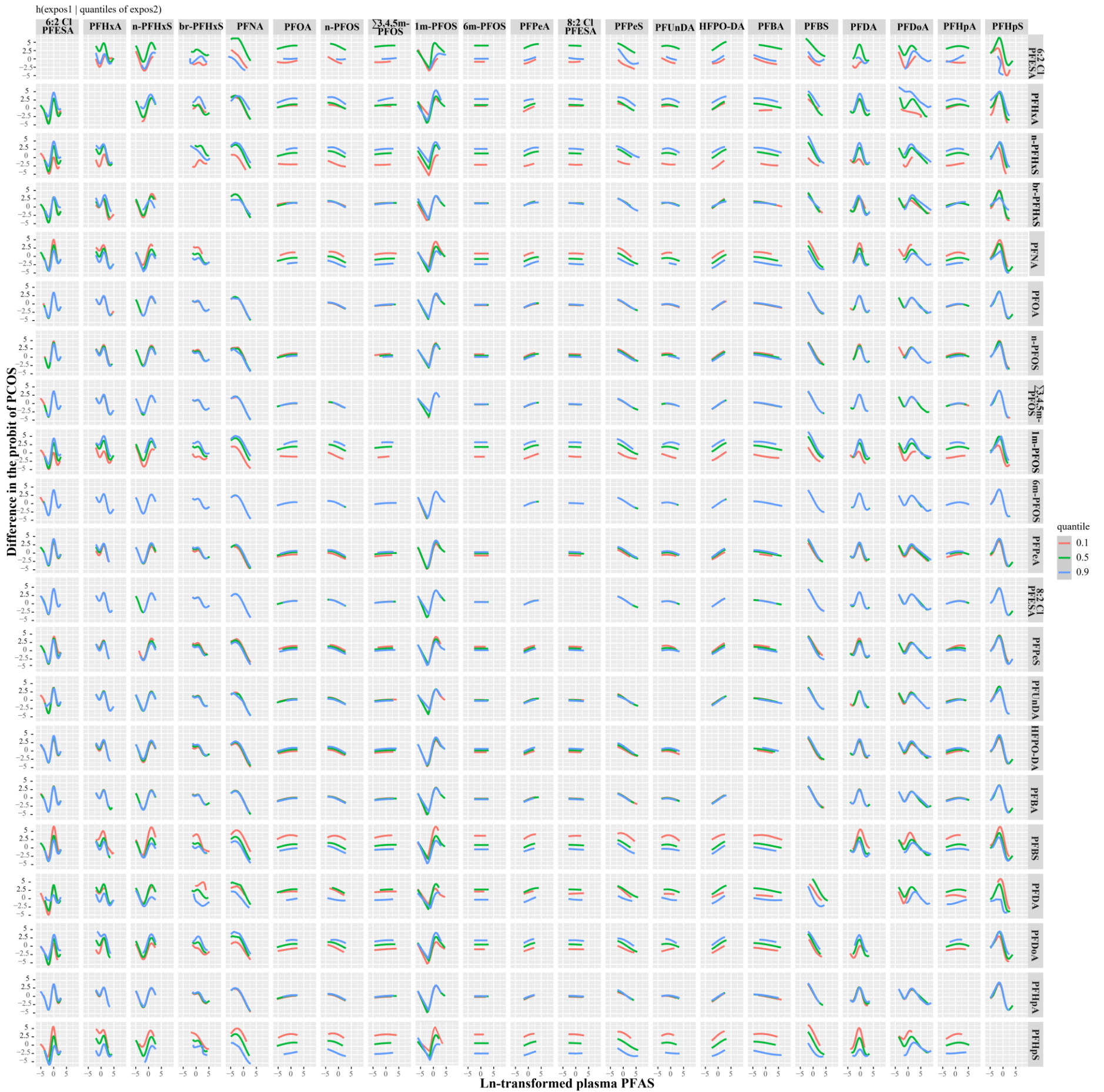
**Fig. S3.** Clustered heatmap of the Spearman correlation matrix of PFAS (ln-transformed) ( $n = 943$ ) (see Excel Tables S1 for corresponding numeric data). The numbers in the box are pairwise correlation coefficients. For full chemical names see Table 1.



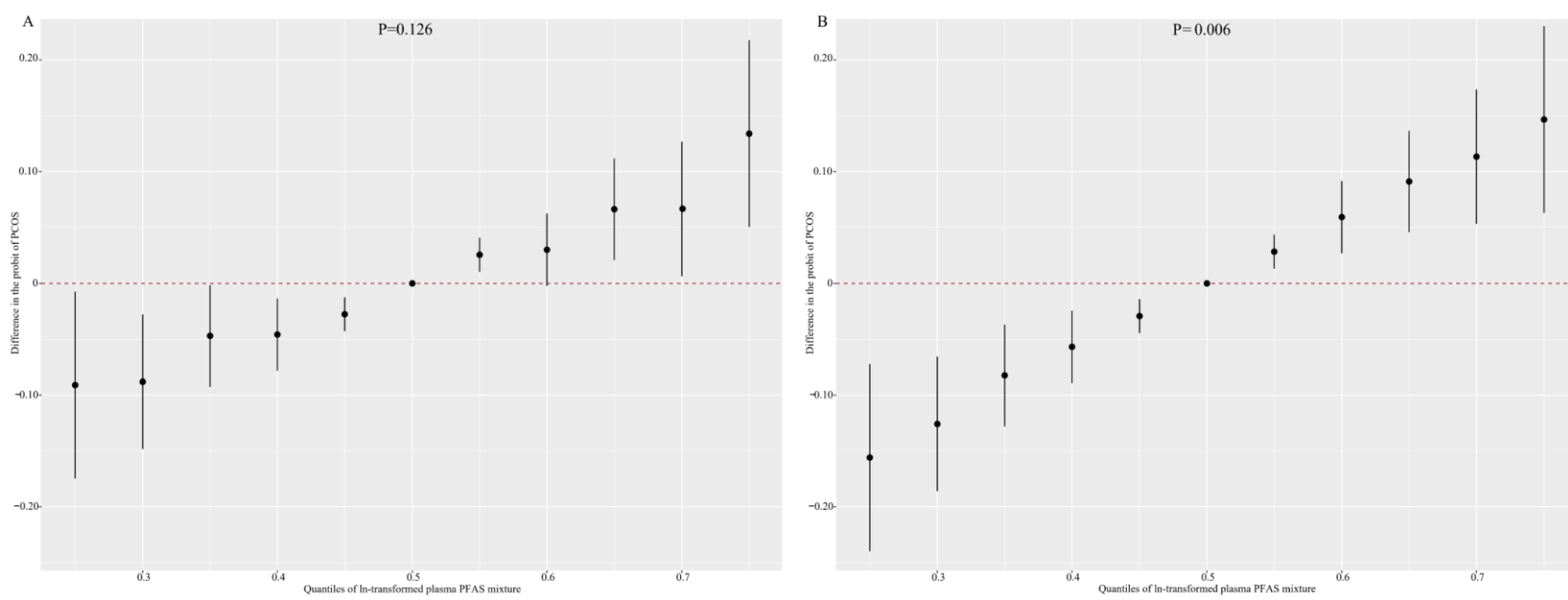




**Fig. S5.** Univariate exposure-response relationship between PFAS and the risk of PCOS (n = 943) (see Excel Tables S4 for corresponding numeric data). Estimates were adjusted for age (linear), BMI (categorical), annual household income (categorical), educational level (categorical), study site (categorical), 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.



**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.