

Supplementary material

Table S1. Persistent endocrine disrupting chemicals measured in maternal serum in the ALSPAC nested case-control study (N=448).

Chemical Name	Abbreviated Name
Per- and Polyfluoroalkyl Substances	
Perfluorooctane sulfonamide	FOSA
2-(N-ethylperfluorooctanesulfonamido) acetate	EtFOSAA
2-(N-methyl-perfluorooctanesulfonamido) acetate	MeFOSAA
Perfluorohexane sulfonate	PFHxS
Perfluorooctane sulfonate	PFOS
Perfluorooctanoate	PFOA
Perfluorononanoate	PFNA
Perfluorodecanoate	PFDA
Polychlorinated Biphenyls	
2,4,4'-trichlorobiphenyl	PCB28
2,2',3,5'-tetrachlorobiphenyl	PCB44
2,2',4,5'-tetrachlorobiphenyl	PCB49
2,2',5,5'-tetrachlorobiphenyl	PCB52
2,3',4,4'-tetrachlorobiphenyl	PCB66
2,4,4',5-tetrachlorobiphenyl	PCB74
2,2',3,4,5'-pentachlorobiphenyl	PCB87
2,2',4,4',5-pentachlorobiphenyl	PCB99
2,2',4,5,5'-pentachlorobiphenyl	PCB101
2,3,3',4,4'-pentachlorobiphenyl	PCB105
2,3,3',4',6-pentachlorobiphenyl	PCB110
2,3',4,4',5-pentachlorobiphenyl	PCB118
2,2',3,3',4,4'-hexachlorobiphenyl	PCB128
2,2',3,4,4',5'-hexachlorobiphenyl and 2,3,3',4,4',6-hexachlorobiphenyl	PCB138-158
2,2',3,4',5,5'-hexachlorobiphenyl	PCB146
2,2',3,4',5',6-hexachlorobiphenyl	PCB149
2,2',3,5,5',6-hexachlorobiphenyl	PCB151
2,2',4,4',5,5'-hexachlorobiphenyl	PCB153
2,3,3',4,4',5-hexachlorobiphenyl	PCB156
2,3,3',4,4',5'-hexachlorobiphenyl	PCB157
2,3',4,4',5,5'-hexachlorobiphenyl	PCB167
2,2',3,3',4,4',5-heptachlorobiphenyl	PCB170
2,2',3,3',4,5,5'-heptachlorobiphenyl	PCB172
2,2',3,3',4',5,6-heptachlorobiphenyl	PCB177
2,2',3,3',5,5',6-heptachlorobiphenyl	PCB178
2,2',3,4,4',5,5'-heptachlorobiphenyl	PCB180
2,2',3,4,4',5',6-heptachlorobiphenyl	PCB183
2,2',3,4',5,5',6-heptachlorobiphenyl	PCB187
2,3,3',4,4',5,5'-heptachlorobiphenyl	PCB189
2,2',3,3',4,4',5,5'-octachlorobiphenyl	PCB194

2,2',3,3',4,4',5,6-octachlorobiphenyl	PCB195
2,2',3,3',4,4',5',6-octachlorobiphenyl and 2,2',3,4,4',5,5',6-octachlorobiphenyl	PCB196-203
2,2',3,3',4,5,6,6'-octachlorobiphenyl	PCB199
2,2',3,3',4,4',5,5',6-nonachlorobiphenyl	PCB206
Decachlorobiphenyl	PCB209

Organochlorine Pesticides

Hexachlorobenzene	HCB
β -Hexachlorocyclohexane	β -HCH
γ -Hexachlorocyclohexane (Lindane)	γ -HCH
Oxychlorane	Oxychlorane
Trans-Nonachlor	Trans-nonachlor
2,2-Bis(4-chlorophenyl)-1,1-dichloroethene	p,p'-DDE
2-(4-chlorophenyl)-2-(2-chlorophenyl)-1,1,1-trichloroethane	o,p'-DDT
2,2-Bis(4-chlorophenyl)-1,1,1-trichloroethane	p,p'-DDT
Mirex	Mirex

Table S2. Characteristics of the Avon Longitudinal Study of Parents and Children (ALSPAC) nested case-control study population by select endocrine disrupting chemicals (N=448 mother-daughter dyads).

Characteristic	PFOA	PCB153	p,p'-DDE
	(ng/mL)	(ng/g lipid)	(ng/g lipid)
	Median (IQR)	Median (IQR)	Median (IQR)
Maternal race			
White	3.8 (2.9–4.8)*	64.8 (48.6–85.8)	308 (193–490)*
Non-white	2.3 (1.6–2.9)*	67.7 (47.4–95.1)	620 (363–1635)*
Maternal education ^a			
< O-level	3.6 (2.8–4.5)	59.7 (45.5–78.6)*	298 (184–472)*
O-level	3.7 (2.9–5.0)	55.9 (44.2–72.3)*	257 (166–460)*
>O-level	3.9 (2.8–4.8)	74.4 (57.8–95.6)*	384 (227–536)*
Maternal age at menarche, years			
8–11	4.0 (3.0–4.9)	68.0 (48.1–90.2)	339 (194–544)
≥12	3.7 (2.8–4.8)	63.5 (48.8–83.6)	308 (192–487)
Maternal pre-pregnancy BMI, kg/m ²			
<25 (under/normal weight)	3.8 (2.8–4.8)	69.0 (51.2–88.1)*	329 (194–513)
≥25 (overweight/obese)	3.7 (3.0–4.8)	57.2 (44.0–77.6)*	306 (211–541)
Prenatal smoking			
Any	3.4 (2.9–4.4)	59.8 (46.0–74.3)	283 (170–412)
None	3.8 (2.8–4.9)	65.7 (48.9–87.5)	323 (200–504)
Physical activity			
Any	3.8 (2.9–5.0)	65.2 (49.9–88.4)	322 (203–504)
None	3.7 (2.9–4.7)	66.3 (46.1–85.2)	316 (187–533)
Maternal age at delivery, years			
<25	3.9 (3.0–4.8)	44.2 (35.0–56.5)*	178 (136–292)*
25–29	3.8 (3.0–4.9)	59.8 (48.1–74.1)*	289 (198–422)*
≥30	3.6 (2.5–4.6)	81.9 (64.3–105.4)*	451 (283–620)*
Child birth order			
First born	4.4 (3.4–5.4)*	63.9 (46.3–84.3)	316 (198–513)
Second born or later	3.1 (2.4–4.0)*	66.9 (50.2–87.5)	323 (193–497)
Child birth weight, g			
<2500	4.1 (3.3–5.6)	74.4 (60.0–102.8)	461 (329–1390)*
≥2500	3.7 (2.8–4.8)	63.7 (47.5–84.5)	302 (185–487)*
Breastfeeding			
Any	3.7 (2.8–4.7)	67.9 (49.4–88.6)*	323 (201–501)
None	4.1 (3.1–5.1)	56.0 (42.4–76.7)*	293 (164–472)
Gestational age at sample, weeks			
<20	4.0 (3.0–5.0)*	65.7 (48.7–84.8)	337 (206–516)*
≥20	3.1 (2.5–4.2)*	60.8 (47.5–86.2)	276 (167–469)*

Abbreviations: g, grams; kg/m², kilograms per meter-squared

^a <O-level=none, Certificate of Secondary Education, and vocational education, which are equivalent to no diploma or a GED in the United States. O-levels (ordinary levels) are required and completed at the age of 16. >O-level=A-levels (advanced levels) completed at 18, which are optional, but required to get

into university; and a university degree.

* Significantly different ($p < 0.05$) using Wilcoxon rank sum test

Table S3. Sensitivity analysis exploring associations of detectable versus below the limit of detection serum concentrations of persistent endocrine disrupting chemicals with early menarche in the Avon Longitudinal Study of Parents and Children (ALSPAC) nested case-control study (N=448 mother-daughter dyads).

	OR (95% CI)^{abc}
Perfluoroalkyl substances (PFAS) (ng/mL)	
PFOA	N/A
PFOS	N/A
PFHxS	N/A
PFNA	N/A
FOSA	1.46 (0.88, 2.42)
MeFOSAA	0.53 (0.27, 1.04)
EtFOSAA	N/A
PFDA	N/A
Polychlorinated biphenyls (PCBs) (ng/g lipid)	
PCB28	1.27 (0.55, 2.95)
PCB44	1.02 (0.61, 1.70)
PCB49	0.75 (0.46, 1.21)
PCB52	1.00 (0.60, 1.67)
PCB66	1.06 (0.63, 1.78)
PCB74	N/A
PCB87	0.75 (0.46, 1.23)
PCB99	N/A
PCB101	0.77 (0.46, 1.29)
PCB105	1.78 (0.73, 4.36)
PCB110	1.04 (0.65, 1.67)
PCB118	N/A
PCB128	0.94 (0.42, 2.11)
PCB138 ^d	N/A
PCB146	N/A
PCB149	0.76 (0.47, 1.24)

PCB151	0.81 (0.45, 1.46)
PCB153	N/A
PCB156	N/A
PCB157	0.88 (0.53, 1.47)
PCB167	1.20 (0.69, 2.08)
PCB170	N/A
PCB172	1.11 (0.63, 1.95)
PCB177	0.63 (0.27, 1.45)
PCB178	0.57 (0.28, 1.16)
PCB180	N/A
PCB183	N/A
PCB187	N/A
PCB189	0.45 (0.26, 0.78)
PCB194	N/A
PCB195	0.74 (0.40, 1.35)
PCB196 ^d	N/A
PCB199	N/A
PCB206	0.52 (0.22, 1.24)
PCB209	0.69 (0.40, 1.20)

Organochlorine pesticides (OCPs) (ng/g lipid)

HCB	N/A
β-HCH	N/A
γ-HCH	0.82 (0.46, 1.45)
Oxychlorane	0.62 (0.35, 1.07)
Trans-nonachlor	0.84 (0.48, 1.46)
p,p'-DDE	N/A
o,p'-DDT	N/A
p,p'-DDT	0.84 (0.40, 1.78)
Mirex	N/A

Abbreviations: OR, odds ratio; CI, confidence interval; ng/mL, nanogram per milliliter; ng/g lipid, nanogram per gram lipid

^a Adjusted for maternal age at menarche, parity, pre-pregnancy BMI, maternal age at delivery, education, prenatal smoking, and gestational age at sample collection

^b Restricted to those with % <LOD between 5% and 95%

^c OR represents the odds of early menarche for those with concentrations above the LOD, compared to those with concentrations below the LOD

^d PCB congeners 138 and 158 could not be separated and were quantified as a summed concentration hereafter referred to as PCB138. Similarly, PCB congeners 196 and 203 could not be separated and were quantified as a summed concentration hereafter referred to as PCB196.

Table S4. Comparison of characteristics of various sub-samples of mother-daughter dyads from the Avon Longitudinal Study of Parents and Children (ALSPAC) population. The nested case-control study (N=448) was drawn from cohort daughters who were actively enrolled at puberty (N=3,913). Complete analytic data for mixture analyses was available for 284 mother-daughter dyads.

Characteristic	Enrolled at Puberty N=3,913 n (%)^a	Nested Case-Control N=448 n (%)^a	Analytic Data N=284 n (%)
Maternal race			
White	3719 (98.2)	423 (98.1)	179 (98.2)
Non-white	68 (1.8)	8 (1.9)	5 (1.8)
Maternal education ^b			
< O-level	712 (19.5)	75 (18.1)	48 (16.9)
O-level	1334 (36.5)	140 (33.7)	95 (33.5)
>O-level	1612 (44.1)	200 (48.2)	141 (49.6)
Maternal age at menarche, years			
8–11	639 (18.7)	93 (23.7)	63 (22.9)
≥12	2785 (81.3)	299 (76.3)	219 (77.1)
Maternal pre-pregnancy BMI			
<25 kg/m ² (under/normal weight)	2876 (80.5)	313 (77.9)	221 (77.1)
≥25 kg/m ² (overweight/obese)	698 (19.5)	89 (22.1)	65 (22.9)
Prenatal smoking			
Any	542 (14.4)	79 (18.5)	44 (15.5)
None	3212 (85.6)	348 (81.5)	240 (84.5)
Maternal age at delivery			
<25 years	646 (16.5)	92 (20.7)	48 (16.9)
25–29 years	1564 (40.0)	164 (36.9)	109 (38.4)
≥30 years	1702 (43.5)	189 (42.5)	127 (44.7)
Child birth order			
First born	1770 (47.3)	208 (49.6)	142 (50.0)
Second born or later	1973 (52.7)	211 (50.4)	142 (50.0)

Abbreviations: g, grams; kg/m², kilograms per meter-squared

^a Missing data not represented

^b <O-level=none, Certificate of Secondary Education, and vocational education, which are equivalent to no diploma or a GED in the United States. O-levels (ordinary levels) are required and completed at the age of 16. >O-level=A-levels (advanced levels) completed at 18, which are optional, but required to get into university; and a university degree.

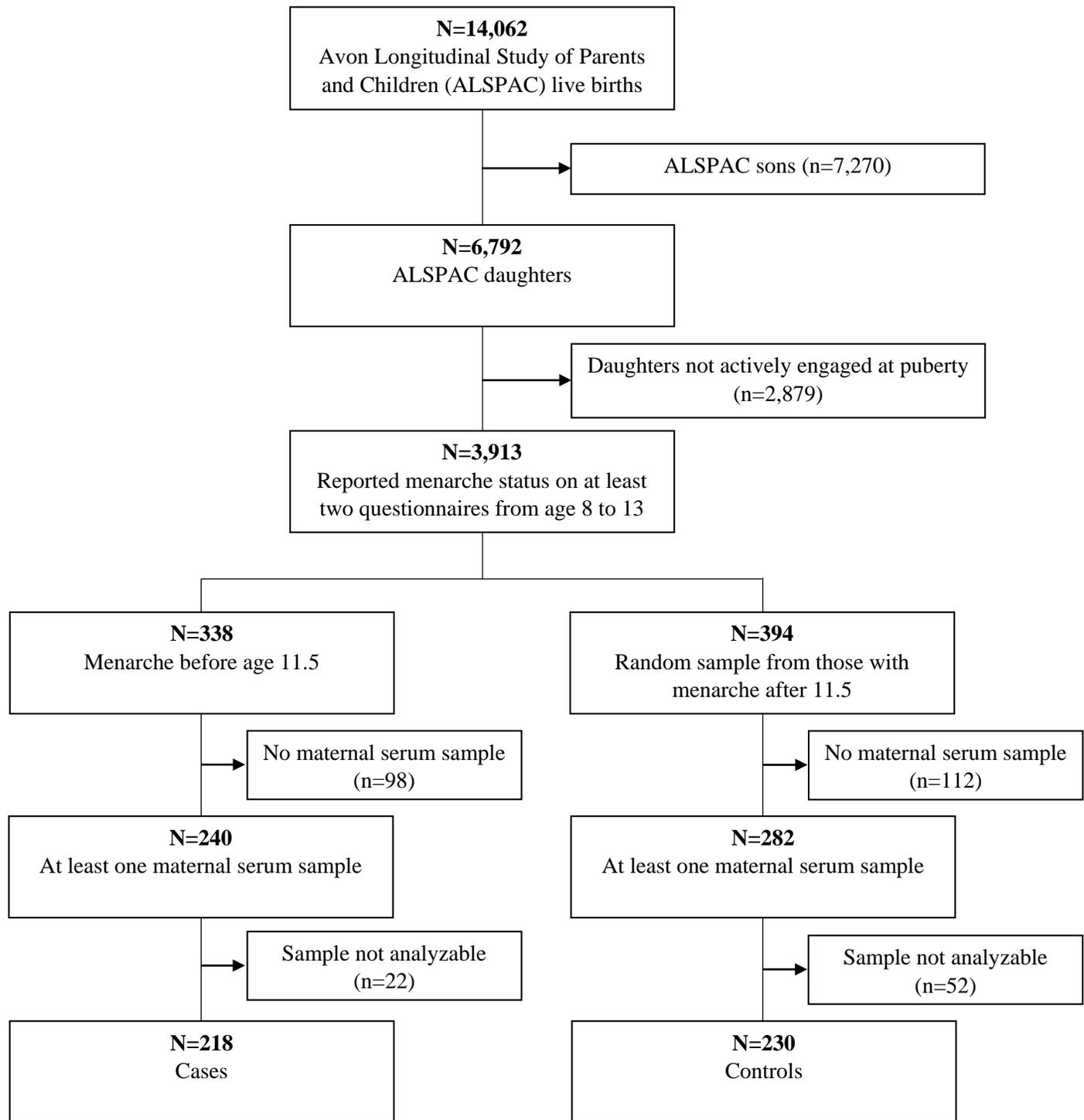


Figure S1. Flowchart of eligibility and exclusions in a nested case-control study of the Avon Longitudinal Study of Parents and Children examining prenatal exposure to endocrine disrupting chemicals with early menarche.

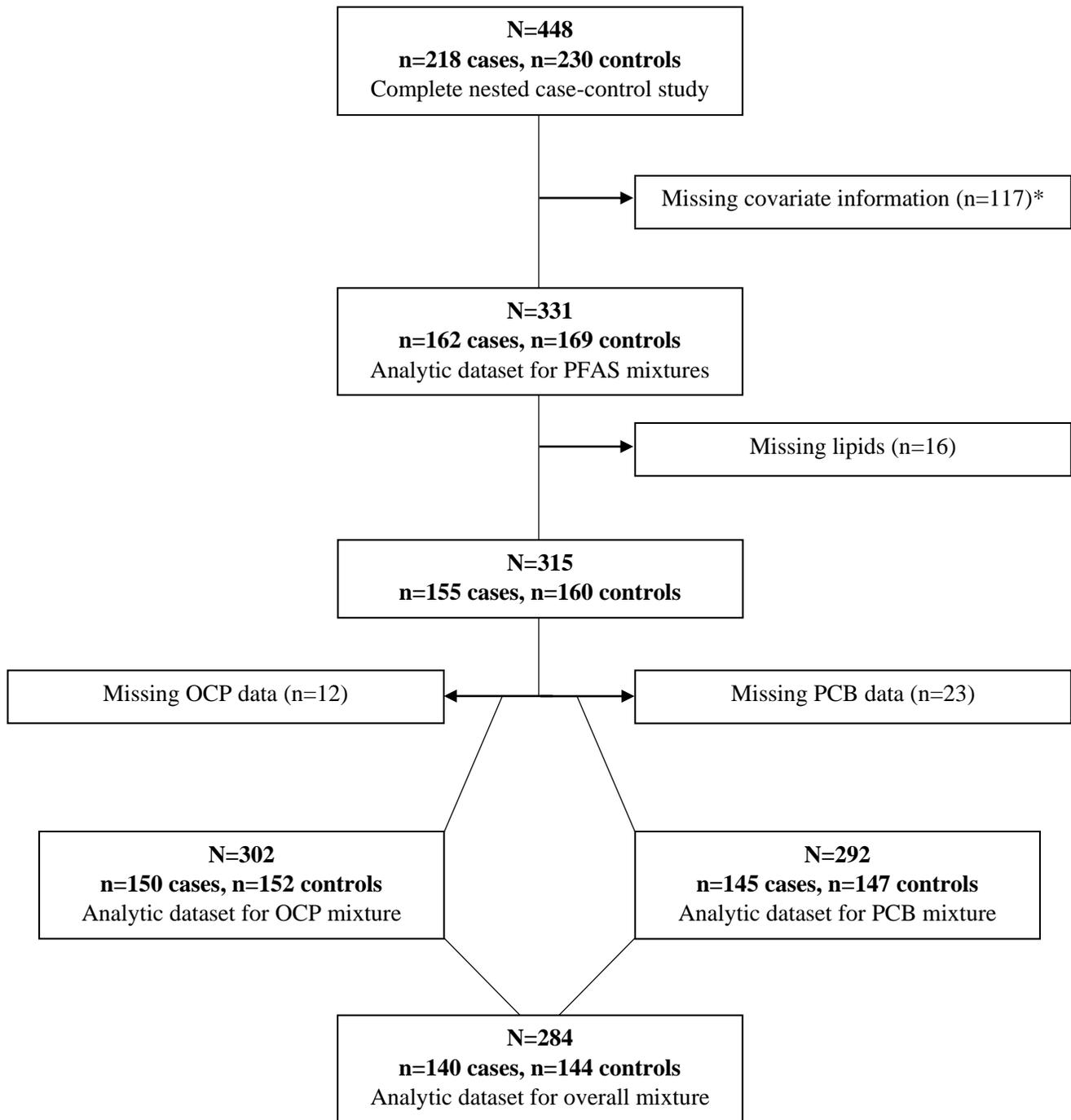


Figure S2. Flowchart depicting missing data in the study of prenatal exposure to mixtures of persistent endocrine disrupting chemicals and early menarche in a nested case-control study of the Avon Longitudinal Study of Parents and Children.

* Data were missing on maternal education (n=33, 7.4%), maternal age at menarche (n=56, 12.5%), maternal pre-pregnancy BMI (n=46, 10.3%), prenatal smoking (n=21, 4.7%), maternal age at delivery (n=3, 0.7%), and child birth order (n=29, 6.5%).

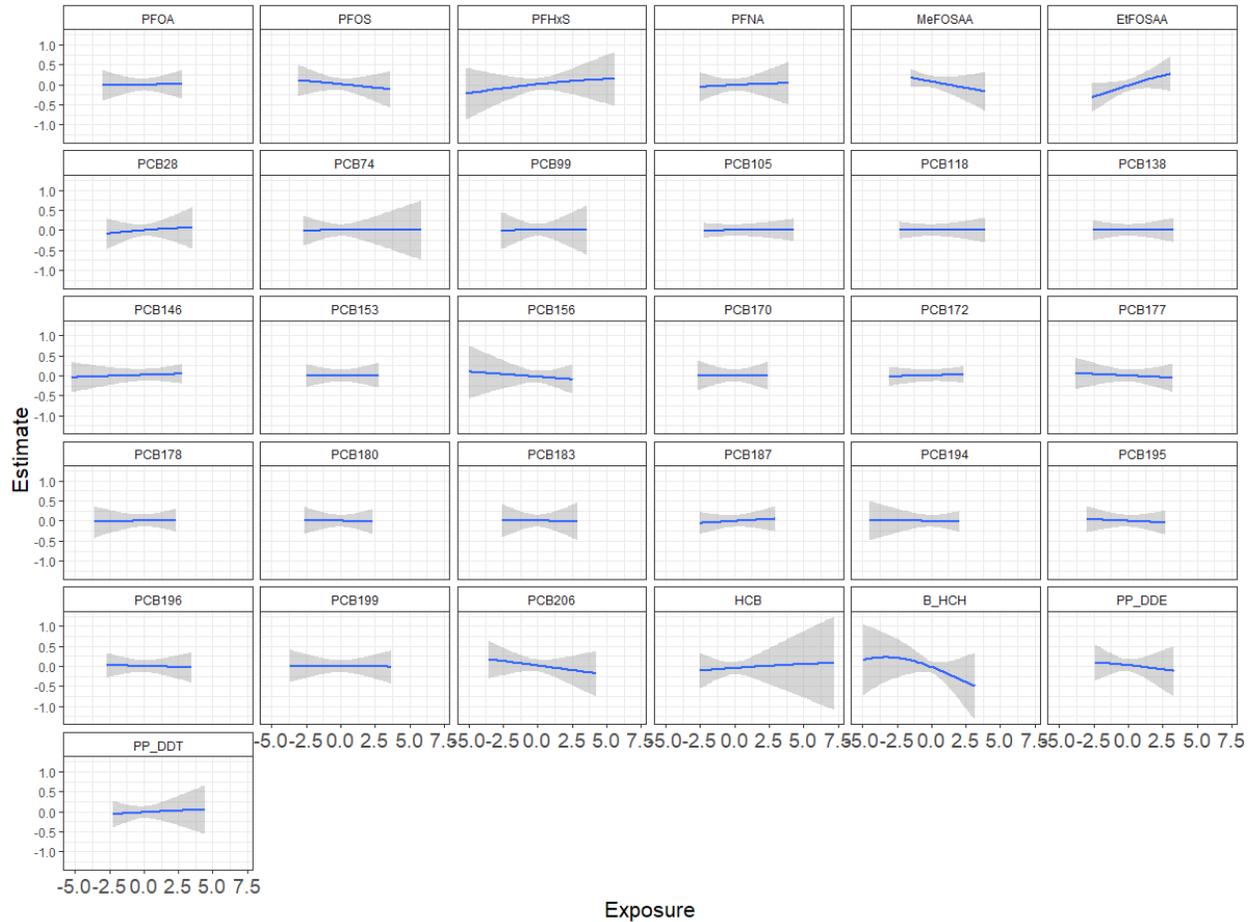


Figure S3. Chemical-specific effect estimates of mixture members (all three classes combined) on early menarche in ALSPAC mother-daughter dyads estimated by Bayesian kernel machine regression (N=284). Single chemical associations and 95% credible bands are presented with other chemicals fixed at their median. The model adjusted for maternal age at menarche, education, parity, pre-pregnancy body mass index, maternal age at delivery, prenatal smoking, and gestational week at sample collection. All chemical concentrations were natural log-transformed and standardized; PCB and OCP concentrations were lipid-adjusted.

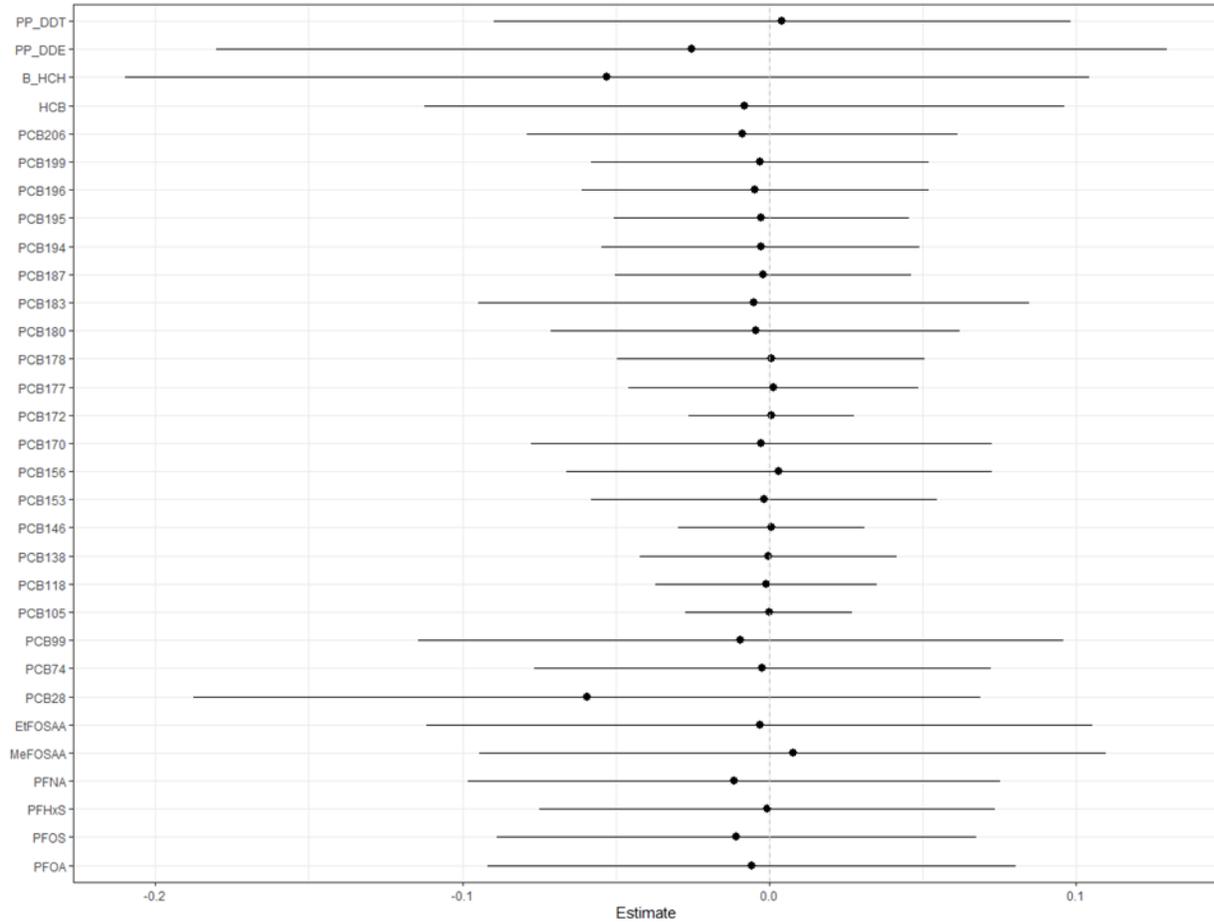


Figure S4. Interaction terms for individual mixture members and the remaining chemicals in ALSPAC mother-daughter dyads estimated by Bayesian kernel machine regression (N=284). Each point represents the difference between the effect size of the chemical when all other chemicals are held at their 75th percentiles and the effect size of the same chemical when all other chemicals are held at their 25th percentiles. Range indicates 95% credible interval. Model adjusted for maternal age at menarche, parity, pre-pregnancy BMI, maternal age at delivery, education, smoking, and gestational age at sample collection. All chemical concentrations were natural log-transformed and standardized; PCBs and OCPs were lipid adjusted.