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Supplemental Material

Prenatal Exposure to Perfluoroalkyl Substances and Cardiometabolic Risk in Children from the Spanish INMA Birth Cohort Study

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Table S1. Summary of maternal PFAS concentrations and outcomes by region of residence in our study.

| Characteristic | Region of residence – [values are n (%) or mean ± SD] | | | p-value ^a |
|----------------------------------|---|----------------|----------------|----------------------|
| | Gipuzkoa | Sabadell | Valencia | |
| From birth until 6 months | | | | |
| Rapid growth | | | | |
| <i>No</i> | 207 (24) | 296 (35) | 349 (41) | <0.01 |
| <i>Yes</i> | 50 (17) | 99 (33) | 153 (51) | |
| Weight-gain z-score | -0.04 ± 0.95 | 0.03 ± 0.98 | 0.21 ± 1.07 | <0.01 |
| At 4 years | | | | |
| BMI (kg/m ²) | 16.43 ± 1.50 | 16.09 ± 1.58 | 16.13 ± 1.69 | <0.01 |
| Overweight | | | | |
| <i>No</i> | 194 (23) | 300 (35) | 361 (42) | <0.01 |
| <i>Yes</i> | 127 (34) | 109 (29) | 139 (37) | |
| WC (cm) | - | 52.07 ± 4.10 | 50.42 ± 4.11 | <0.01 |
| Systolic BP (mmHg) | - | 102.25 ± 12.46 | 102.82 ± 17.74 | 0.60 |
| Diastolic BP (mmHg) | - | 65.44 ± 12.17 | 66.42 ± 17.48 | 0.36 |
| TC (mg/dL) | 164.47 ± 24.60 | 165.88 ± 27.51 | 174.97 ± 26.49 | <0.01 |
| HDL-C (mg/dL) | 45.10 ± 11.22 | 52.26 ± 10.15 | 58.49 ± 11.82 | <0.01 |
| LDL-C (mg/dL) | 101.86 ± 20.32 | 97.30 ± 22.11 | 105.36 ± 22.96 | <0.01 |
| TG (mg/dL) | 87.55 ± 38.31 | 81.58 ± 38.26 | 54.39 ± 19.17 | <0.01 |
| At 7 years | | | | |
| BMI (kg/m ²) | 17.43 ± 2.36 | 16.86 ± 2.47 | 17.60 ± 2.81 | <0.01 |
| Overweight | | | | |
| <i>No</i> | 230 (32) | 254 (35) | 236 (33) | <0.01 |
| <i>Yes</i> | 50 (14) | 128 (35) | 188 (51) | |
| WC (cm) | 58.03 ± 5.37 | 57.80 ± 6.79 | 58.74 ± 7.02 | <0.01 |
| Systolic BP (mmHg) | 107.39 ± 11.52 | 106.87 ± 12.32 | 111.73 ± 11.14 | <0.01 |
| Diastolic BP (mmHg) | 63.96 ± 11.89 | 62.54 ± 12.40 | 66.00 ± 10.12 | <0.01 |
| Maternal PFAS (ng/mL) | | | | |
| PFHxS | 0.48 ± 0.21 | 0.95 ± 0.68 | 0.60 ± 0.28 | <0.01 |
| PFOS | 5.89 ± 2.65 | 6.84 ± 3.46 | 6.41 ± 2.62 | <0.01 |
| PFOA | 1.95 ± 1.19 | 3.22 ± 2.00 | 2.70 ± 1.47 | <0.01 |
| PFNA | 0.68 ± 0.37 | 0.91 ± 0.42 | 0.65 ± 0.37 | <0.01 |

Abbreviations: SD: standard deviation; BMI: body mass index; BP: blood pressure; WC: waist circumference; PFHxS: perfluorohexanesulfonic acid; PFOS: perfluorooctanesulfonic acid; PFOA: perfluorooctanoic acid; PFNA: perfluorononanoic acid.

^aP-values correspond to the following: Analysis of variance (ANOVA) for continuous variables, and chi-squared test for categorical variables.

Table S2. Details of the imputation modeling.

| |
|--|
| Software used and key setting: STATA 14.0 software (Stata Corporation, College Station, Texas) – Ice command (with 10 cycles) |
| Number of imputed datasets created: 20 |
| Variables included in the imputation procedure: <i>Variables used in the main analyses (outcome, exposure, and potential confounders)</i> Maternal concentrations of PFHxS, PFOS, PFOA, PFNA at 12 weeks of pregnancy. Maternal characteristics (age, country of birth, previous breastfeeding, pre-pregnancy BMI, region of residence, type of residence zone, education, smoking during pregnancy, passive smoking during pregnancy, social class, fish intake during pregnancy, weight gain during pregnancy, gestational diabetes mellitus, and gestational week at blood sample collection) Child characteristics (sex, age at follow-up, height at follow-up, type of delivery, birth weight, duration of any breastfeeding). |
| Treatment of non-normally distributed variables: log-transformed |
| Treatment of binary/categorical variables: logistic, ordinal, and multinomial models |
| Statistical interactions included in imputation models: none, but we performed multiple imputation separately by age at follow-up (6 months, 4 years, and 7 years) and region of residence (Gipuzkoa, Sabadell, and Valencia) |

Table S3. Example of summary of characteristics in the observed and the imputed datasets corresponding to the 4-year-old population from the region of Sabadell.

| Maternal characteristics | % of missing | Observed | Imputed |
|--|---------------------|-----------------|----------------|
| PFHxS (ng/mL) – mean | 2.3 | 1.0 | 0.9 |
| PFNA (ng/mL) - mean | 0.8 | 0.9 | 0.9 |
| Gestational age at blood sampling (weeks) - mean | 0.5 | 13.5 | 13.5 |
| Parity (number of pregnancies) - % | 0.5 | 0.5 | 0.5 |
| Previous breastfeeding (total number of weeks of all previous pregnancies) - mean | 0.5 | 12.3 | 12.4 |
| Pre-pregnancy BMI (kg/m ²) - mean | 1.0 | 25.8 | 25.8 |
| Weight gain during pregnancy (kg) - mean | 2.9 | 14.4 | 14.3 |
| Smoking at the beginning of pregnancy (cigarettes per day) - mean | 1.3 | 3.9 | 4.0 |
| Country of birth - % | 0.3 | | |
| <i>Spain</i> | | 90.6 | 90.8 |
| <i>Latin American</i> | | 7.3 | 7.3 |
| <i>Europe</i> | | 1.8 | 1.8 |
| Education - % | 0.5 | | |
| <i>Primary or without education</i> | | 24.0 | 24.4 |
| <i>Secondary</i> | | 43.3 | 43.5 |
| <i>University</i> | | 32.1 | 32.1 |
| Type of delivery - % | 1.8 | | |
| <i>Vaginal</i> | | 64.2 | 65.3 |
| <i>Instrumental</i> | | 19.1 | 19.5 |
| <i>Cesarean</i> | | 14.9 | 15.2 |

Abbreviations: PFHxS: perfluorohexanesulfonic acid; PFNA: perfluorononanoic acid; BMI: body mass index

Table S4. Summary of characteristics in the excluded and the included samples in our study.

| Characteristic | 6 months | | | 4 years-overall | | | 4 years- lipid analysis | | | 4 years- CM-score analysis | | | 7 years | | |
|--|--------------------|----------------------|--------------------------|--------------------|----------------------|--------------------------|-------------------------|---------------------|--------------------------|----------------------------|---------------------|--------------------------|---------------------|----------------------|--------------------------|
| | Excluded (n=89) | Included (n=1154) | p- value ^a | Excluded (n=13) | Included (n=1230) | p- value ^a | Excluded (n=603) | Included (n=627) | p- value ^a | Excluded (n=844) | Included (n=386) | p- value ^a | Excluded (n=157) | Included (n=1086) | p- value ^a |
| Child | | | | | | | | | | | | | | | |
| Sex of the child - n (%) | | | | | | | | | | | | | | | |
| <i>Girls</i> | 36 (40) | 568 (49) | 0.11 | 4 (31) | 600 (49) | 0.20 | 321 (53) | 309 (49) | 0.17 | 441 (52) | 189 (49) | 0.28 | 69 (44) | 535 (49) | 0.27 |
| <i>Boys</i> | 53 (60) | 586 (51) | | 9 (69) | 630 (51) | | 282 (47) | 318 (51) | | 403 (48) | 197 (51) | | 88 (56) | 551 (51) | |
| Birth weight (g)- mean ± SD | 3355 ± 467 | 3254 ± 460 | 0.05 | 3419 ± 491 | 3260 ± 460 | 0.22 | 3246 ± 466 | 3272 ± 455 | 0.34 | 3259 ± 460 | 3263 ± 462 | 0.88 | 3293 ± 509 | 3257 ± 453 | 0.98 |
| Maternal | | | | | | | | | | | | | | | |
| PFOS (ng/mL)- mean ± SD | 6.16 ± 3.13 | 6.42 ± 2.94 | 0.42 | 5.30 ± 2.59 | 6.42 ± 2.96 | 0.17 | 6.40 ± 3.03 | 6.44 ± 2.89 | 0.80 | 6.32 ± 3.01 | 6.63 ± 2.82 | 0.08 | 6.05 ± 2.81 | 6.46 ± 2.97 | 0.08 |
| PFOA (ng/mL)- mean ± SD | 2.14 ± 1.26 | 2.71 ± 1.69 | 0.00 | 2.09 ± 0.94 | 2.68 ± 1.68 | 0.21 | 2.71 ± 1.53 | 2.65 ± 1.81 | 0.52 | 2.59 ± 1.80 | 2.85 ± 1.37 | 0.01 | 2.51 ± 1.46 | 2.69 ± 1.70 | 0.01 |
| Age (years)- mean ± SD | 31.10 ± 3.67 | 30.69 ± 4.05 | 0.35 | 28.08 ± 3.52 | 30.75 ± 4.02 | 0.02 | 30.51 ± 4.07 | 30.98 ± 3.96 | 0.04 | 30.86 ± 3.95 | 30.51 ± 4.17 | 0.16 | 30.52 ± 4.34 | 30.75 ± 3.98 | 0.21 |
| Fish intake (servings per week) - mean ± SD | 5.77 ± 3.01 | 4.91 ± 2.55 | 0.00 | 4.81 ± 1.89 | 4.97 ± (2.60) | 0.83 | 4.84 ± 2.56 | 5.09 ± 2.63 | 0.09 | 4.97 ± 2.56 | 4.98 ± 2.68 | 0.93 | 5.08 ± 2.93 | 4.95 ± 2.54 | 0.94 |
| Region of residence-n (%) | | | | | | | | | | | | | | | |
| <i>Gipuzkoa</i> | 67 (75) | 257 (22) | 0.00 | 3 (23) | 321 (26) | 0.07 | 119 (20) | 202 (32) | < 0.01 | 321 (38) | 0 (0) | < 0.01 | 44 (28) | 280 (26) | <0.01 |
| <i>Sabadell</i> | 15 (17) | 395 (34) | | 1 (8) | 409 (33) | | 143 (24) | 266 (42) | | 176 (21) | 233 (60) | | 28 (18) | 382 (35) | |
| <i>Valencia</i> | 7 (8) | 502 (44) | | 9 (69) | 500 (41) | | 341 (57) | 159 (25) | | 347 (41) | 153 (40) | | 85 (54) | 424 (39) | |
| Country of birth-n (%) | | | | | | | | | | | | | | | |
| <i>Spain</i> | 83 (94) | 1074 (93) | 0.67 | 11 (85) | 1146 (93) | 0.22 | 568 (94) | 578 (92) | 0.23 | 798 (95) | 348 (91) | 0.01 | 137 (87) | 1020 (94) | 0.02 |
| <i>Other</i> | 5 (6) | 79 (7) | | 2 (15) | 82 (7) | | 35 (6) | 47 (8) | | 46 (5) | 36 (9) | | 20 (13) | 64 (6) | |
| Previous breastfeeding - n (%)^b | | | | | | | | | | | | | | | |
| <i>Never</i> | 44 (49) | 708 (61) | 0.08 | 7 (54) | 745 (61) | 0.81 | 390 (65) | 355 (57) | 0.01 | 524 (62) | 221 (58) | 0.48 | 86 (55) | 666 (61) | 0.52 |
| <i>Short-term (<4 months)</i> | 9 (10) | 125 (11) | | 1 (8) | 133 (11) | | 67 (11) | 66 (11) | | 86 (10) | 47 (12) | | 20 (13) | 114 (11) | |
| <i>Long-term (4-6 months)</i> | 12 (13) | 97 (8) | | 1 (8) | 108 (9) | | 47 (8) | 61 (10) | | 72 (9) | 36 (9) | | 16 (10) | 93 (9) | |

| | | | | | | | | | | | | | | | |
|--|---------|----------|------|---------|----------|------|----------|----------|-------|----------|----------|-------|----------|----------|-------|
| <i>months)</i> | | | | | | | | | | | | | | | |
| <i>Very-long-term (>6 months)</i> | 24 (27) | 222 (19) | | 4 (31) | 242 (20) | | 99 (16) | 143 (23) | | 162 (19) | 80 (21) | | 35 (22) | 211 (19) | |
| Parity (number of pregnancies) -n (%) | | | | | | | | | | | | | | | |
| <i>None</i> | 39 (44) | 657 (57) | 0.05 | 5 (38) | 691 (56) | 0.22 | 360 (60) | 331 (53) | 0.04 | 487 (58) | 204 (53) | 0.25 | 74 (47) | 622 (57) | 0.33 |
| <i>One</i> | 42 (47) | 423 (37) | | 8 (62) | 457 (37) | | 203 (34) | 254 (41) | | 301 (36) | 156 (41) | | 63 (40) | 402 (37) | |
| <i>Two or more</i> | 8 (9) | 72 (6) | | 0 (0) | 80 (7) | | 40 (7) | 40 (6) | | 56 (7) | 24 (6) | | 20 (13) | 60 (6) | |
| Pre-pregnancy BMI (kg/m²) -n (%) | | | | | | | | | | | | | | | |
| <i>Underweight</i> | 5 (6) | 49 (4) | 0.55 | 0 (0) | 54 (4) | 0.33 | 26 (4) | 28 (4) | 0.53 | 40 (5) | 14 (4) | 0.07 | 4 (3) | 50 (5) | 0.06 |
| <i>Normal weight</i> | 65 (73) | 796 (69) | | 12 (92) | 849 (69) | | 427 (71) | 422 (67) | | 598 (71) | 251 (65) | | 118 (75) | 743 (68) | |
| <i>Overweight</i> | 15 (17) | 214 (19) | | 1 (8) | 228 (19) | | 107 (18) | 121 (19) | | 145 (17) | 83 (22) | | 20 (13) | 209 (19) | |
| <i>Obese</i> | 4 (4) | 95 (8) | | 0 (0) | 99 (8) | | 43 (7) | 56 (9) | | 61 (7) | 38 (10) | | 15 (10) | 84 (8) | |
| Education-n (%) | | | | | | | | | | | | | | | |
| <i>Primary or without education</i> | 14 (16) | 269 (23) | 0.02 | 5 (38) | 278 (23) | 0.21 | 132 (22) | 146 (23) | 0.70 | 173 (21) | 105 (27) | <0.01 | 41 (26) | 242 (22) | <0.01 |
| <i>Secondary</i> | 32 (36) | 489 (42) | | 6 (46) | 515 (42) | | 260 (43) | 255 (41) | | 344 (41) | 171 (45) | | 75 (48) | 446 (41) | |
| <i>University</i> | 43 (48) | 393 (34) | | 2 (15) | 434 (35) | | 211 (35) | 223 (36) | | 326 (39) | 108 (28) | | 40 (26) | 396 (37) | |
| Smoking at the beginning of pregnancy-n (%) | | | | | | | | | | | | | | | |
| <i>No</i> | 63 (71) | 782 (68) | 0.56 | 9 (69) | 836 (68) | 1.00 | 386 (64) | 450 (72) | <0.01 | 564 (67) | 272 (70) | 0.20 | 94 (60) | 751 (69) | 0.19 |
| <i>Yes</i> | 26 (29) | 372 (32) | | 4 (31) | 394 (32) | | 217 (36) | 177 (28) | | 280 (33) | 114 (30) | | 63 (40) | 335 (31) | |

Abbreviations: SD: standard deviation; PFOS: perfluorooctanesulfonic acid; PFOA: perfluorooctanoic acid; BMI: body mass index.

^a a P-values correspond to the following: Analysis of variance (ANOVA) for continuous variables, and chi squared or Fisher`s exact test for categorical variables.

^b b Breastfeeding duration: never, short-term [<4 months], long-term [4-6 months], and very long-term [>6 months].

Table S5. Associations between maternal PFAS concentrations (log₂-transformed, in ng/mL) and anthropometric binary outcomes during childhood.

| Anthropometric measurement | n | Relative Risk (95% CI) | | | |
|----------------------------------|------|------------------------|-------------------|-------------------|-------------------|
| | | PFHxS | PFOS | PFOA | PFNA |
| From birth until 6 months | | | | | |
| Rapid growth | 1154 | | | | |
| <i>Unadjusted</i> | | 1.00 (0.89, 1.11) | 0.99 (0.87, 1.14) | 1.09 (0.96, 1.23) | 0.98 (0.87, 1.10) |
| <i>Adjusted</i> | | 0.91 (0.80, 1.03) | 0.92 (0.80, 1.06) | 0.99 (0.86, 1.14) | 0.97 (0.85, 1.11) |
| At 4 years | | | | | |
| Overweight | 1230 | | | | |
| <i>Unadjusted</i> | | 0.92 (0.84, 1.01) | 1.00 (0.88, 1.13) | 0.98 (0.88, 1.09) | 1.03 (0.93, 1.15) |
| <i>Adjusted</i> | | 0.96 (0.87, 1.07) | 1.08 (0.94, 1.23) | 1.06 (0.94, 1.20) | 1.08 (0.96, 1.21) |
| WHtR>0.5 ^b | 839 | | | | |
| <i>Unadjusted</i> | | 1.05 (0.91, 1.21) | 0.92 (0.78, 1.09) | 1.07 (0.91, 1.25) | 1.06 (0.91, 1.24) |
| <i>Adjusted</i> | | 0.96 (0.83, 1.11) | 0.97 (0.82, 1.15) | 1.01 (0.85, 1.20) | 1.01 (0.86, 1.18) |
| At 7 years | | | | | |
| Overweight | 1086 | | | | |
| <i>Unadjusted</i> | | 1.04 (0.94, 1.15) | 1.00 (0.88, 1.13) | 1.11 (1.00, 1.24) | 1.01 (0.90, 1.13) |
| <i>Adjusted</i> | | 0.94 (0.84, 1.05) | 0.96 (0.84, 1.10) | 1.01 (0.89, 1.15) | 1.06 (0.93, 1.20) |
| WHtR>0.5 | 1086 | | | | |
| <i>Unadjusted</i> | | 1.16 (0.98, 1.36) | 1.08 (0.88, 1.32) | 1.15 (0.99, 1.35) | 1.14 (0.97, 1.34) |
| <i>Adjusted</i> | | 0.97 (0.81, 1.17) | 1.05 (0.84, 1.31) | 0.96 (0.79, 1.16) | 1.11 (0.93, 1.34) |

Abbreviations: PFHxS: perfluorohexanesulfonic acid; PFOS: perfluorooctanesulfonic acid; PFOA: perfluorooctanoic acid; PFNA: perfluorononanoic acid; BMI: body mass index; WHtR: Waist-to-height ratio.

^c Model adjusted by: maternal characteristics (i.e. region of residence, country of birth, previous breastfeeding, age and pre-pregnancy BMI) and the age and sex of the child.

^d Only Sabadell and Valencia subcohorts have available data for this outcome.

*Note: Coefficients represent the average difference in the outcome with a doubling of the exposure.

Table S6. Unadjusted associations between maternal PFAS concentrations (log₂-transformed, in ng/mL) and cardio-metabolic components during childhood.

| Cardio-metabolic components | n | β (95 % CI) | | | |
|----------------------------------|------|---------------------|---------------------|---------------------|---------------------|
| | | PFHxS | PFOS | PFOA | PFNA |
| From birth until 6 months | | | | | |
| Weight gain z-score | 1154 | -0.01 (-0.08, 0.06) | 0.04 (-0.05, 0.12) | 0.09 (0.02, 0.17) | 0.01 (-0.07, 0.08) |
| At 4 years | | | | | |
| BMI z-score | 1230 | -0.05 (-0.12, 0.02) | -0.01 (-0.10, 0.07) | -0.01 (-0.08, 0.07) | 0.02 (-0.05, 0.09) |
| WC z-score ^a | 839 | -0.02 (-0.11, 0.06) | -0.06 (-0.14, 0.04) | 0.01(-0.08, 0.10) | 0.01 (-0.07, 0.09) |
| BP z-score ^{a, b} | 839 | -0.03 (-0.11, 0.05) | -0.07 (-0.17, 0.03) | -0.07 (-0.17, 0.02) | -0.02 (-0.11, 0.06) |
| Lipids (mg/dL) | | | | | |
| TC z-score | 627 | 0.00 (-0.09, 0.08) | -0.01 (-0.13, 0.11) | 0.00 (-0.11, 0.10) | -0.01 (-0.12, 0.09) |
| HDL-C z-score | 627 | -0.02 (-0.10, 0.06) | -0.06 (-0.17, 0.05) | -0.05 (-0.15, 0.04) | -0.04 (-0.14, 0.06) |
| LDL-C z-score | 627 | -0.02 (-0.10, 0.07) | 0.00 (-0.11, 0.12) | 0.02 (-0.08, 0.12) | 0.00 (-0.11, 0.10) |
| Triglycerides z-score | 627 | 0.07 (-0.01, 0.15) | 0.04 (-0.06, 0.15) | 0.03 (-0.07, 0.12) | 0.03 (-0.07, 0.12) |
| CM-risk score | 386 | 0.39 (-0.08, 0.86) | 0.11 (-0.48, 0.71) | 0.62 (0.03, 1.20) | 0.92 (0.38, 1.46) |
| At 7 years | | | | | |
| BMI z-score | 1086 | -0.03 (-0.12, 0.05) | 0.00 (-0.11, 0.11) | 0.01 (-0.08, 0.11) | 0.01 (-0.09, 0.10) |
| WC z-score | 1086 | -0.01 (-0.08, 0.07) | -0.02 (-0.11, 0.07) | -0.01 (-0.08, 0.07) | 0.02 (-0.06, 0.10) |
| BP z-score ^b | 1086 | 0.02 (-0.05, 0.09) | 0.01 (-0.08, 0.10) | -0.02 (-0.10, 0.06) | -0.01 (-0.09, 0.07) |

Abbreviations: CI: confidence interval; PFHxS: perfluorohexanesulfonic acid; PFOS: perfluorooctanesulfonic acid; PFOA: perfluorooctanoic acid; PFNA: perfluorononanoic acid; BMI: body mass index; BP: blood pressure; WC: waist circumference; TC: total cholesterol; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein; CM: cardio-metabolic

^e Only Sabadell and Valencia subcohorts have available data for this outcome.

^f BP is the average of SBP and DBP values.

^g CM-risk score is the z-scores for WC, BP, and the mean of the HDL-C and TG z-scores, with HDL-C multiplied -1.

*Note: Coefficients represent the average difference in the outcome with a doubling of the exposure.

Table S7. Complete case analysis for the associations between maternal PFAS concentrations (log₂-transformed, in ng/mL) and cardio-metabolic components during childhood.

| Cardio-metabolic components | n | β (95 % CI) ^a | | | |
|----------------------------------|------|--------------------------------|---------------------|---------------------|---------------------|
| | | PFHxS | PFOS | PFOA | PFNA |
| From birth until 6 months | | | | | |
| Weight gain z-score | 1110 | -0.09 (-0.19, 0.02) | -0.02 (-0.13, 0.08) | 0.05 (-0.04, 0.14) | 0.02 (-0.08, 0.11) |
| At 4 years | | | | | |
| BMI z-score | 1178 | 0.01 (-0.09, 0.11) | 0.07 (-0.03, 0.17) | 0.07 (-0.02, 0.16) | 0.09 (0.00, 0.18) |
| WC z-score ^b | 813 | -0.07 (-0.18, 0.04) | -0.03 (-0.15, 0.08) | 0.01 (-0.09, 0.12) | 0.04 (-0.06, 0.14) |
| BP z-score ^{b,c} | 813 | -0.01 (-0.13, 0.10) | -0.05 (-0.17, 0.07) | -0.07 (-0.18, 0.04) | -0.03 (-0.15, 0.08) |
| Lipids z-scores | | | | | |
| TC | 600 | 0.04 (-0.10, 0.17) | 0.06 (-0.09, 0.20) | 0.06 (-0.07, 0.18) | 0.05 (-0.08, 0.18) |
| HDL-C | 600 | -0.01 (-0.13, 0.12) | -0.02 (-0.15, 0.12) | -0.01 (-0.13, 0.11) | 0.02 (-0.10, 0.14) |
| LDL-C | 600 | 0.01 (-0.13, 0.14) | 0.06 (-0.08, 0.21) | 0.06 (-0.06, 0.19) | 0.05 (-0.08, 0.18) |
| Triglycerides | 600 | 0.12 (-0.01, 0.24) | 0.03 (-0.10, 0.16) | 0.03 (-0.09, 0.15) | 0.01 (-0.11, 0.13) |
| CM-risk score ^d | 375 | -0.38 (-1.00, 0.24) | 0.01 (-0.70, 0.72) | 0.10 (-0.57, 0.76) | 0.45 (-0.21, 1.11) |
| At 7 years | | | | | |
| BMI z-score | 1042 | 0.00 (-0.12, 0.13) | 0.10 (-0.02, 0.23) | 0.05 (-0.06, 0.16) | 0.11 (-0.01, 0.22) |
| WC z-score | 1042 | -0.02 (-0.12, 0.09) | 0.06 (-0.04, 0.17) | -0.01 (-0.10, 0.08) | 0.04 (-0.06, 0.13) |
| BP z-score ^c | 1042 | 0.06 (-0.05, 0.16) | 0.04 (-0.07, 0.15) | -0.04 (-0.14, 0.05) | -0.03 (-0.12, 0.07) |

Abbreviations: CI: confidence interval; PFHxS: perfluorohexanesulfonic acid; PFOS: perfluorooctanesulfonic acid; PFOA: perfluorooctanoic acid; PFNA: perfluorononanoic acid; BMI: body mass index; BP: blood pressure; WC: waist circumference; TC: total cholesterol; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein; CM: cardio-metabolic.

^h Model adjusted by: maternal characteristics (i.e. region of residence, country of birth, previous breastfeeding, age and pre-pregnancy BMI) and the age and sex of the child.

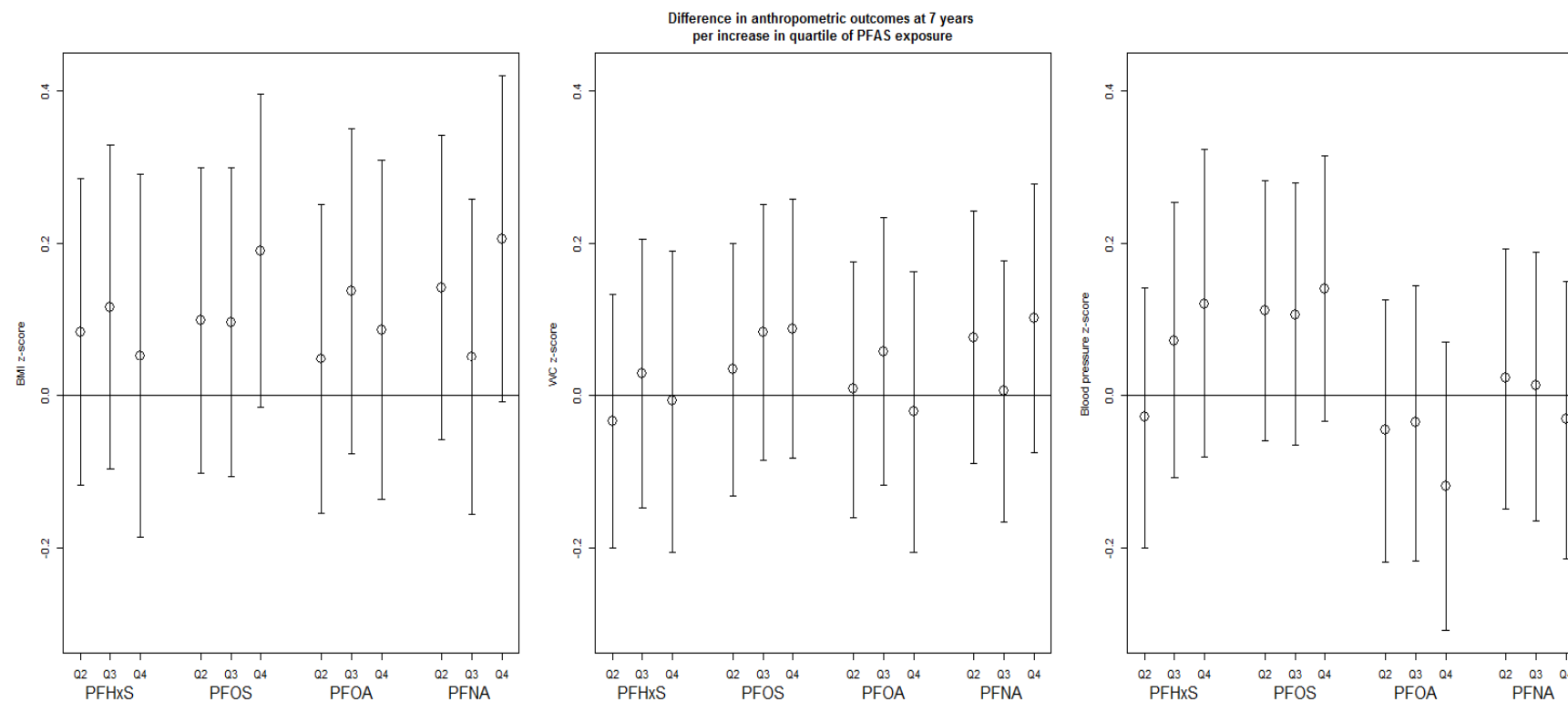
ⁱ Only Sabadell and Valencia subcohorts have available data for this outcome.

^j BP is the average of SBP and DBP values.

^k CM-risk score is the z-scores for WC, BP, and the mean of the HDL-C and TG z-scores, with HDL-C multiplied -1.

Note: Coefficients represent the average difference in the outcome with a doubling of the exposure.

Figure S1. Associations between quartiles of maternal PFAS concentrations (\log_2 -transformed, in ng/mL) and anthropometric measurements, and blood pressure at age 7 years (n=1086).



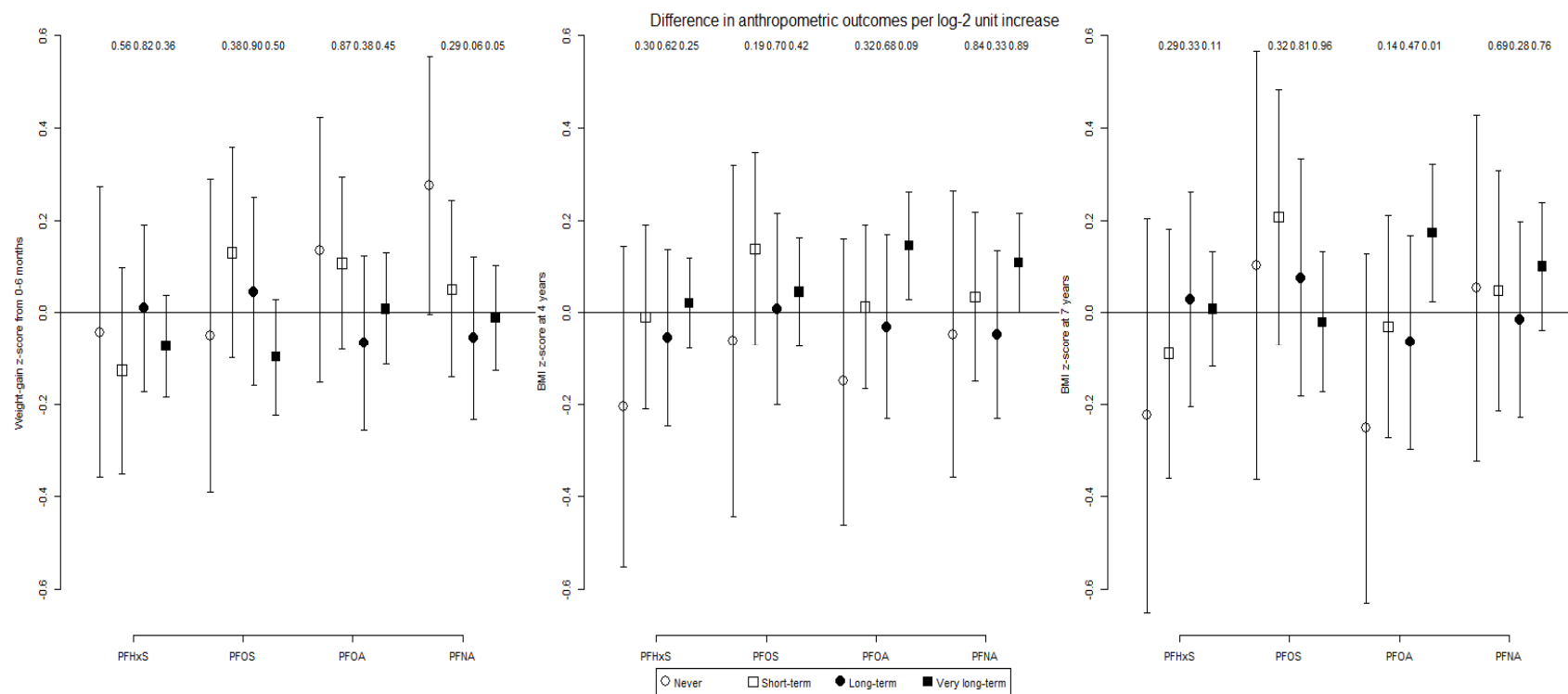
Abbreviations: CI: confidence interval; PFHxS: perfluorohexanesulfonic acid; PFOS: perfluorooctanesulfonic acid; PFOA: perfluorooctanoic acid; PFNA: perfluorononanoic acid; BMI: body mass index; WC: waist circumference; BP: blood pressure; Q1-Q4: quartiles 1, 2, 3, and 4.

^a Model adjusted by: maternal characteristics (i.e. region of residence, country of birth, previous breastfeeding, age and pre-pregnancy BMI) and the age and sex of the child.

^b BP is the average of SBP and DBP values.

*Note: We report associations between quartiles of PFAS exposure and outcomes only at age 7 years because of evidence of departures from linearity based on GAMs. Coefficients represent the average difference in the outcome with a doubling of the exposure.

Figure S2. Adjusted associations between maternal PFAS concentrations (\log_2 -transformed, in ng/mL) and weight gain, and BMI z-scores by breastfeeding duration for the index child.



Abbreviations: PFHxS: perfluorohexanesulfonic acid; PFOS: perfluorooctanesulfonic acid; PFOA: perfluorooctanoic acid; PFNA: perfluorononanoic acid; BMI: body mass index.

^a Model adjusted by: maternal characteristics (i.e. region of residence, country of birth, previous breastfeeding, age and pre-pregnancy BMI) and the age and sex of the child.

^b Breastfeeding duration: never, short-term [<4 months], long-term [4-6 months], and very long-term [>6 months].

*Note: Coefficients represent the average difference in the outcome with a doubling of the exposure. Values at the top are the p-values for the breastfeeding of the index child-interaction term.

Table S8. Associations between maternal PFAS concentrations (log₂-transformed, in ng/mL) and weight gain, and BMI z-scores after adjustment for maternal glomerular filtration rate.

| Anthropometric outcome | n | β (95 % CI) ^a | | | |
|----------------------------------|-----|--------------------------------|---------------------|---------------------|---------------------|
| | | PFHxS | PFOS | PFOA | PFNA |
| From birth until 6 months | | | | | |
| Weight-gain z-score | 732 | -0.09 (-0.21, 0.04) | -0.03 (-0.15, 0.09) | 0.03 (-0.08, 0.14) | -0.03 (-0.14, 0.08) |
| At 4 years | | | | | |
| BMI z-score | 800 | 0.06 (-0.06, 0.18) | 0.10 (-0.01, 0.21) | 0.09 (-0.02, 0.19) | 0.05 (-0.06, 0.15) |
| WC z-score ^b | 497 | -0.03 (-0.18, 0.11) | 0.03 (-0.11, 0.17) | 0.00 (-0.14, 0.13) | -0.04 (-0.18, 0.10) |
| BP z-score ^{b, c} | 469 | 0.03 (-0.10, 0.17) | 0.00 (-0.13, 0.13) | -0.02 (-0.14, 0.11) | -0.05 (-0.19, 0.08) |
| At 7 years | | | | | |
| BMI z-score | 720 | -0.01 (-0.16, 0.15) | 0.00 (-0.14, 0.14) | 0.03 (-0.10, 0.16) | 0.01 (-0.12, 0.15) |
| WC z-score | 718 | -0.01 (-0.14, 0.11) | -0.05 (-0.16, 0.07) | -0.01 (-0.12, 0.10) | 0.01 (-0.11, 0.12) |
| BP z-score ^c | 714 | 0.08 (-0.05, 0.22) | 0.03 (-0.10, 0.15) | -0.02 (-0.13, 0.10) | -0.04 (-0.16, 0.08) |

Abbreviations: PFHxS: perfluorohexanesulfonic acid; PFOS: perfluorooctanesulfonic acid; PFOA: perfluorooctanoic acid; PFNA: perfluorononanoic acid; BMI: body mass index.

^a Model adjusted by: maternal characteristics (i.e. region of residence, country of birth, previous breastfeeding, age, pre-pregnancy BMI, and glomerular filtration rate) and the age and sex of the child.

^b Only Sabadell and Valencia subcohorts have available data for this outcome.

^c BP is the average of SBP and DBP values.

*Note: Coefficients represent the average difference in the outcome with a doubling of the exposure.

Table S9. Associations between maternal PFAS concentrations (log₂-transformed, in ng/mL) and weight gain, and BMI z-scores after adjustment for maternal albumin level.

| Anthropometric outcome | n | β (95 % CI) ^a | | | |
|----------------------------------|-----|--------------------------------|---------------------|---------------------|---------------------|
| | | PFHxS | PFOS | PFOA | PFNA |
| From birth until 6 months | | | | | |
| Weight-gain z-score | 732 | -0.09 (-0.21, 0.04) | -0.03 (-0.15, 0.08) | 0.02 (-0.09, 0.13) | -0.03 (-0.14, 0.08) |
| At 4 years | | | | | |
| BMI z-score | 800 | 0.06 (-0.07, 0.18) | 0.10 (-0.01, 0.20) | 0.08 (-0.02, 0.19) | 0.04 (-0.06, 0.15) |
| WC z-score ^b | 497 | -0.04 (-0.18, 0.11) | 0.02 (-0.12, 0.16) | 0.00 (-0.13, 0.14) | -0.05 (-0.19, 0.09) |
| BP z-score ^{b,c} | 469 | 0.03 (-0.11, 0.16) | 0.00 (-0.13, 0.12) | -0.02 (-0.15, 0.11) | -0.06 (-0.19, 0.08) |
| At 7 years | | | | | |
| BMI z-score | 720 | -0.01 (-0.16, 0.14) | 0.00 (-0.14, 0.14) | 0.03 (-0.10, 0.16) | 0.01 (-0.12, 0.15) |
| WC z-score | 718 | -0.01 (-0.14, 0.11) | -0.05 (-0.16, 0.06) | -0.01 (-0.12, 0.10) | 0.00 (-0.11, 0.11) |
| BP z-score ^c | 714 | 0.08 (-0.05, 0.21) | 0.02 (-0.10, 0.14) | -0.02 (-0.13, 0.09) | -0.04 (-0.16, 0.07) |

Abbreviations: PFHxS: perfluorohexanesulfonic acid; PFOS: perfluorooctanesulfonic acid; PFOA: perfluorooctanoic acid; PFNA: perfluorononanoic acid; BMI: body mass index.

^a Model adjusted by: maternal characteristics (i.e. region of residence, country of birth, previous breastfeeding, age, pre-pregnancy BMI, and plasma albumin levels) and the age and sex of the child.

^b Only Sabadell and Valencia subcohorts have available data for this outcome.

^c BP is the average of SBP and DBP values.

*Note: Coefficients represent the average difference in the outcome with a doubling of the exposure.

Table S10. Associations between maternal PFAS concentrations (log₂-transformed, in ng/mL) and continuous anthropometric outcomes and blood pressure in children not born by cesarean section.

| Cardio-metabolic components | n | β (95 % CI) ^a | | | |
|----------------------------------|------|--------------------------------|---------------------|---------------------|---------------------|
| | | PFHxS | PFOS | PFOA | PFNA |
| From birth until 6 months | | | | | |
| Weight gain z-score | 940 | -0.04 (-0.13, 0.05) | -0.02 (-0.12, 0.08) | 0.07 (-0.02, 0.16) | 0.02 (-0.07, 0.11) |
| At 4 years | | | | | |
| BMI z-score | 1012 | -0.02 (-0.10, 0.07) | 0.05 (-0.05, 0.15) | 0.06 (-0.03, 0.14) | 0.09 (0.01, 0.18) |
| WC z-score ^b | 677 | -0.03 (-0.14, 0.07) | -0.03 (-0.14, 0.09) | 0.03 (-0.08, 0.13) | 0.04 (-0.06, 0.14) |
| BP z-score ^{b, c} | 677 | 0.00 (-0.11, 0.11) | -0.02 (-0.14, 0.1) | -0.06 (-0.18, 0.05) | -0.02 (-0.12, 0.09) |
| At 7 years | | | | | |
| BMI z-score | 891 | -0.06 (-0.16, 0.05) | 0.00 (-0.12, 0.12) | 0.04 (-0.07, 0.15) | 0.09 (-0.02, 0.20) |
| WC z-score | 891 | -0.06 (-0.14, 0.03) | -0.04 (-0.14, 0.06) | 0.00 (-0.09, 0.09) | 0.03 (-0.06, 0.12) |
| BP z-score ^c | 891 | 0.06 (-0.03, 0.15) | 0.06 (-0.04, 0.16) | 0.00 (-0.09, 0.10) | 0.01 (-0.08, 0.11) |

Abbreviations: CI: confidence interval; PFHxS: perfluorohexanesulfonic acid; PFOS: perfluorooctanesulfonic acid; PFOA: perfluorooctanoic acid; PFNA: perfluorononanoic acid; BMI: body mass index; WC: waist circumference, and BP: blood pressure;

^a Model adjusted by: maternal characteristics (i.e. region of residence, country of birth, previous breastfeeding, age and pre-pregnancy BMI), and the age and sex of the child. Children born by cesarean section were excluded from this analysis.

^b Only Sabadell and Valencia subcohorts have available data for this outcome.

^c BP is the average of SBP and DBP values.

*Note: Coefficients represent the average difference in the outcome with a doubling of the exposure.