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PFAS exposure during pregnancy: Implications for placental health and functioning

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ABSTRACT

Background: Animal studies have linked prenatal poly- and perfluoroalkyl substances (PFAS) exposures with impaired placental structure and function. In humans, only few studies have investigated such associations.
Objective: We studied whether PFAS, individually and as a mixture, affected placental function.
Methods: In 367 pregnant women, we quantified 13 PFAS in serum collected at 19.3 gestational weeks (median). Placental weight was recorded at delivery. Histological examination of placental tissues allowed estimation of vascular perfusion (percentage of villi with syncytial knots, capillary density, intervillous space) and placental aging (fibrin deposition, calcification). Associations between PFAS and each of these parameters were assessed using adjusted linear, logistic regressions and mixture modeling through cluster analysis and Bayesian kernel machine regression (BKMR).
Results: PFHxPA quantification (yes versus no) was associated with an increase in the percentages of villi with syncytial knots (β = 6.0% [95% CI: 1.1; 11]) and reduced intervillous spaces (β = 4.7% [95% CI: 0.1; 9.3]). A similar pattern was observed with PFHpA. Isolated associations were observed between PFTrDA and percentages of villi with syncytial knots (β = 8.6% [95% CI: 2.2; 15]) and 6:2diPAP and capillary density (β = −17% [95% CI: −30; −4.6]). Cluster analysis suggested that women in the moderate-to-higher PFAS exposure group had on average lower placental weight (β= −30 g [95% CI: −56; −4.3]), compared to those in the lower exposure group.
Conclusions: Pregnancy PFAS levels were associated with placental parameters of fetal-maternal exchange, highlighting their broad physiological impacts.

Abbreviations: br-PFHxS, branched- perfluotohexane sulfonic acid; CI, confidence interval; LOD, limit of detection; LOQ, limit of quantification; OR, odds ratio; PFAS, poly- and perfluoroalkyl substances; PFBS, perfluorobutane sulfonic acid; PFDA, perfluorodecanoic acid; PFDoDA, perfluorododecanoic acid; PFHpA, perfluoroheptanoic acid; PFHpS, perfluoroheptane sulfonic acid; PFHxPA, perfluorohexyl phosphonic acid; PFHxS, perfluotohexane sulfonic acid; PFNA, perfluorononaoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFTrDA, perfluorotridecanoic acid; PFUnDA, perfluoroundecanoic acid; PFPeA, perfluoropentanoic acid; 6:2Cl-PFESA, 6:2 chlorinated polyfluorinated ether sulfonic acid; 6:2 diPAP, 6:2 fluorotelomer phosphate diester; PFR, placental-to-fetal ratio; FPR, fetal-to-placental ratio; HPLC, high performance liquid chromatography; MS, mass spectrometry; BKMR, Bayesian kernel machine regression; DOHaD, Developmental Origins of Health and Disease; GW, Gestational Weeks.

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1. Introduction

The placenta is essential during pregnancy, serving as a connection between the mother and the fetus, facilitating nutrient and gas exchange, and functioning as an endocrine and metabolic unit (Burton and Fowden, 2015). Placental weight and placental to fetal weight ratio (PFR) are indicators of placental health and efficiency. PFR reflects the adequacy of fetal nutrition provided by the placenta's functional tissue and placental weight strongly predicts birthweight (Nascente et al., 2020). Placentomegaly (excessive placental growth) has been linked to adverse outcomes like low Apgar scores and respiratory distress (Sathasivam et al., 2023), while placental hypoplasia (low placental weight) has been associated with fetal malformations (Nascente et al., 2020; Salavati et al., 2018; Sathasivam et al., 2023). Placental histology and structure are also key indicators of placental health. Commonly assessed histological parameters at term include markers of maternal and fetal vascular perfusion and placental aging. Dysregulation of these markers has been associated with pregnancy complications such as preeclampsia, fetal growth restriction, and preterm birth (Heerema-McKenney et al., 2019; Khong et al., 2016).

Changes in placental parameters can also signal adaptations to environmental insults (Barker et al., 2010). Environmental factors potentially affecting the placenta include per- and polyfluoroalkyl substances (PFAS), which are a class of synthetic chemicals characterized by their environmental persistence (Brunn et al., 2023). As reviewed in Supplementary Material, Table S1, perfluorooctanesulfonic acid (PFOS) and perfluotohexane sulfonic acid (PFHxS) exposure led to reduced placental weight in rodents (Lee et al., 2015; Li et al., 2016), while for perfluorooctanoic acid (PFOA) both decreasing (Suh et al., 2011) and increasing (Blake et al., 2020) placental weights with higher doses have been reported in mice. Decreased fetal to placental weight (FPR) ratio has also been reported with exposure to PFOA, PFOS in rodents, and with perfluorobutanesulfonic acid (PFBS) in rabbits (Blake et al., 2020; Crute et al., 2023; Suh et al., 2011). Regarding histopathological parameters, PFOA exposure led to fibrin clot formation (Blake et al., 2020), appearance of necrotic zones (Suh et al., 2011), and reduced labyrinth area, the area of fetal maternal exchange (Blake et al., 2020). Similarly, PFOS caused necrotic changes (Lee et al., 2015), while PFHxS exposure lead to a reduction in the labyrinth area and a decrease in the number of blood vessels (Yao et al., 2023; Zhang et al., 2023) (See details in Supplementary Material, Table S1).

Despite growing evidence from toxicological studies, only few epidemiological studies (Chowdhury et al., 2024; Fei et al., 2008; Gan et al., 2024) have investigated the relationship between PFAS exposure and placental weight (reviewed in Supplementary Material, Table S2). Among these, one study with a large sample size (N = 1,400) reported no association between PFOA or PFOS and placental weight (Fei et al., 2008). The Ma'anshan Birth Cohort (N = 712) reported positive associations between exposure to a mixture of 12 PFAS, as well as two individual PFAS (branched perfluorohexane sulfonate (br-PFHxS) and 6:2 chlorinated polyfluorinated ether sulfonate (6:2Cl-PFESA)) with placental weight (Gan et al., 2024). Finally another study examining 14 PFAS found an inverse association between perfluorononanoic acid (PFNA) and placental weight, as well as positive associations between PFNA, perfluorodecanoic acid (PFDA) and FPR (Chowdhury et al., 2024).

Given toxicological studies suggesting harmful effects of PFAS on placenta, and the limited number of human studies on this topic, we aimed to investigate the effects of PFAS exposure on human placental health and functioning. We considered both macroscopic (placental weight and placental-fetal ratio) and microscopic measures (five histological parameters related to placental aging and vascular perfusion).

2. Methods

2.1. Study design and population

We relied on SEPAGES cohort (Lyon-Caen et al., 2019), in which 484 pregnant women were enrolled between July 2014 and July 2017. Women were eligible if they met the following criteria: being less than 19 weeks pregnant at enrollment, aged 18 or older, fluent in reading and speaking French, affiliated with the French national health insurance system, and planning to give birth in one of the four maternity clinics in the Grenoble region. Individuals with multiple pregnancies were excluded. The majority of participants (90 %) were recruited by a field worker during visits to obstetrical ultrasound clinics in the Grenoble area, while the remaining 10 % joined after encountering the SEPAGES brochure in medical facilities. Participants provided written informed consent and study approvals were obtained from the "Comité de Protection des Personnes (CPP Sud-Est)" and the "Commission Nationale de l'Informatique et des Libertés (CNIL)". The current study focuses on a subsample of women with PFAS concentrations assessed in blood collected during pregnancy and placental weight (N = 340) or placental histology (N = 367) evaluated at birth.

2.2. Placental outcomes

2.2.1. Placental weight and PFR

SEPAGES women were given a collection kit to bring to the maternity clinic at the time of delivery (several kits were also distributed to the maternities in case the women forgot to bring their kit at delivery). The kit contained instructions (previously circulated to all participating clinics) for weighing the placenta and collecting placental tissue. Placental weight and tissues collection was done at delivery by medical staff. Newborn weight was extracted from medical records, allowing computation of PFR (Jovanovic et al., 2024) expressed as a percentage using the following formula:

$$\text{PFR} = \frac{\text{Placental weight (g)}}{\text{Birth weight (g)}} \times 100$$

2.2.2. Placental histology

After placental expulsion, tissue from the fetal side (approximately two centimeters from the cord insertion) was taken by medical staff, using a biopsy punch (diameter, 5 mm). The sample was rinsed with physiological serum and then immersed in a tube containing formalin solution (Sigma Aldrich, Formalin Solution Neutral Buffered 10 %). It was stored at 4 °C until being transported to the biobank (CHU Grenoble Alpes, bb-0033–00069). Upon reception, the sample was transferred into a tube containing 1.9 ml of 75 % ethanol, stored at 4 °C. Placental tissues were fixed with buffered formalin 4 %, dehydrated, and embedded in paraffin to prepare Formalin-Fixed Paraffin-Embedded (FFPE) samples, which were used for histopathological analysis. Sections (5 μm) were stained with hematoxylin and eosin and histological paremeters were quantified using an Axioplan microscope (Zeiss) with Axiovision software for image analysis. The quantification method was validated collegially with pathologists from Grenoble hospital and single blinded quantification was then performed by one experienced histopathology technician (NL). This evaluation was conducted on all available placenta.

As part of our quality control, five randomly selected samples were re-examined once a week during the reading period. This method allows verifying that the variations between two readings do not to exceed 10 % for all the studied parameters.

2.2.2.1. Histological markers of maternal vascular malperfusion. Reduction of intervillous space: Placental changes associated with maternal vascular malperfusion include the formation of focal infarct area. No infarct areas were observed in our cohort. However, as infarct areas are characterized by collapsed villi with no intervillous space and loss of

villous structure, we used reductions in intervillous space as an indicator of this processs. The intervillous space is the space between chorionic villi that contains maternal blood. In our study, intervillous space closure was assessed via a score ranging from 0 % (normal placenta) to 100 % (representing a total collapse of the intervillous space, Fig. 1). Higher percentages were considered suggestive of reduced exchange that could potentially lead to fetal hypoxia (Kingdom et al., 2000) and an increased risk of intrauterine growth retardation (Burton and Jauniaux, 2018).

Quantification of villi with syncytial knots: Syncytial knots were defined as a cluster of at least five trophoblast cells agglutinated at the periphery of chorionic villi. Such clusters are observed in normal pregnancies as part of the turnover process that leads to trophoblast apoptosis. However, an elevated number of syncytial knots can indicate placental malperfusion and hypoxia (Soares et al., 2017), which may lead to the development of pregnancy pathologies such as pregnancy hypertension (Burton et al., 2019), pre-eclampsia (Yu et al., 2022), maternal anemia (Kadyrov et al., 2006, 2003), and prolonged pregnancy (Carroll et al., 2022). We calculated the percentage of chorionic villi with at least one syncytial knot, and ranging from 0 % (no villi with syncytial knots) to 100 % (all villi with at least one syncytial knot, Fig. 1).

2.2.2.2. Histological markers of fetal perfusion. Capillary density: In mature intermediate villi of term placentas, vascularization is considered normal when vascular structures occupy a surface area that does not exceed 50 % of the total surface of the villi (Huppertz, 2008). To determine the fetal capillary density, we thus relied on this threshold of 50 %. Higher percentages may reflect a compensatory mechanism to improve fetal maternal exchanges that has been observed in pre-eclampsia, fetal growth restriction, and/or fetal thrombotic vasculopathy (Vafaei et al., 2021). Conversely, lower percentages can be seen as an inhibition of the angiogenesis process that could lead to compromising placental blood flow and fetal nourishment (Chowdhury et al., 2024; Gude et al., 2004). The percentage of villi with more than 50 % of their space filled by capillaries was recorded (Fig. 1).

2.2.2.3. Histological markers of placental aging. Fibrin deposition on chorionic and stem villi: Fibrin deposition refers to the accumulation of fibrin, an insoluble protein from the fibrinogen involved in the blood clotting. Fibrin deposition increases with gestational age (Moser et al., 2019). Fibrin inside or around chorionic villi may lead to the villi deterioration and decreased fetal-maternal exchanges and has been linked to prematurity and intrauterine growth retardation (Devisme et al., 2017; Kim et al., 2019; Lampi et al., 2022; Spinillo et al., 2019). We assessed fibrin deposition without distinguishing between intra- or inter- villous locations, using a 0 to 100 % scoring system (Fig. 2).

Placental calcification: the deposition of calcium in the placenta, tipically occurs in late pregnancy, as part of the natural aging process (Poggi et al., 2001). Excessive calcification, however, can impair maternal-fetal exchanges. The degree of calcification was assessed with the Placental Calcification Score (PCS) proposed by Rossi et al. (Rossi et al., 2019) (Fig. 2, details in Supplementary Material). A PCS > 10, was considered as elevated value and used to binarized this outcome.

2.3. Prenatal PFAS exposure

Non-fasting maternal blood samples were collected by trained field workers (median, 19.3 gestational weeks (GW), 25 – 75th percentiles: 18 – 20.9 GW)) and stored at −80 °C. One serum aliquot was shipped to the Norwegian Institute of Public Health for assessments of 26 PFAS (See Supplementary Material, Table 3 for a detailed list). The PFAS analyzed were those for which validated analytical methods were available (Haug et al., 2009; Poothong et al., 2017). These included the most prevalent

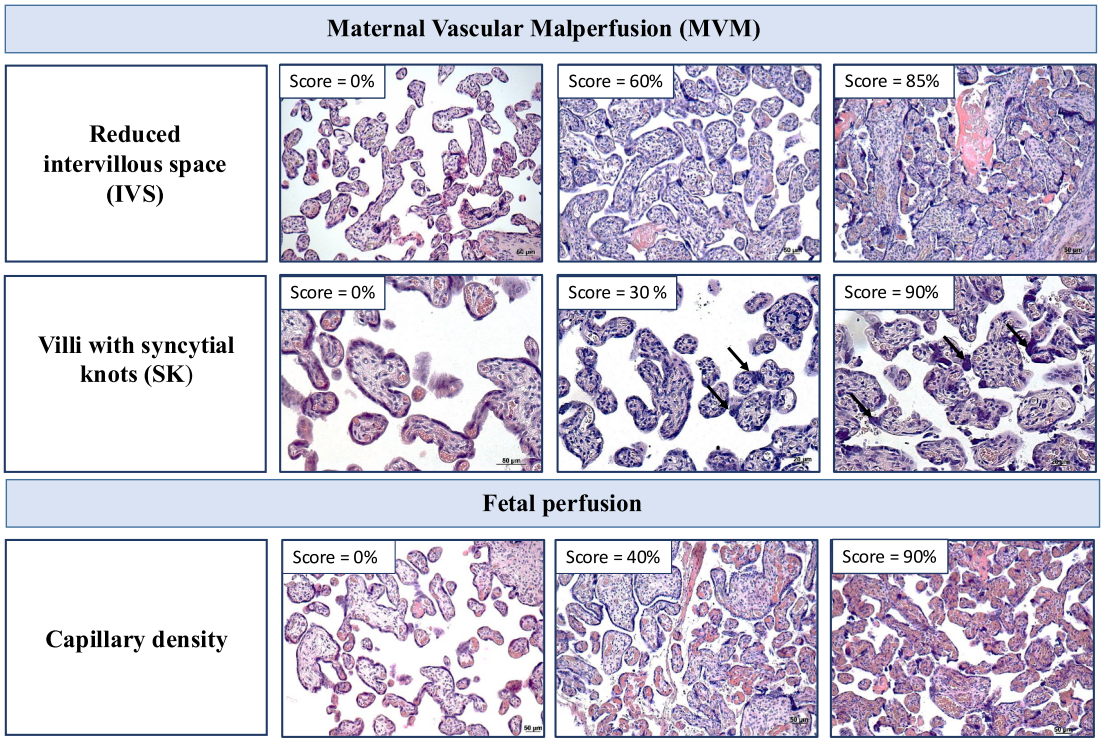

Fig. 1. Representation of the scoring method used to quantify placental parameters of Maternal Vascular Malperfusion and Fetal Perfusion in SEPAGES Representative photographs of the ranges of scoring used to classify the degree of maternal vascular malperfusion (MVM) and fetal perfusion. Reduced Intervillous Space refers to percentage of closure of the intervillous space, quantified as % and serves as an indicator of fetal maternal exchange dynamics. Villi with syncytial knots refers to percentage of villi with trophoblastic nuclear clusters. Capillary density refers to the density or quantity of the microvascular fetal capillary networks within the mature intermediate villi, quantified as %.

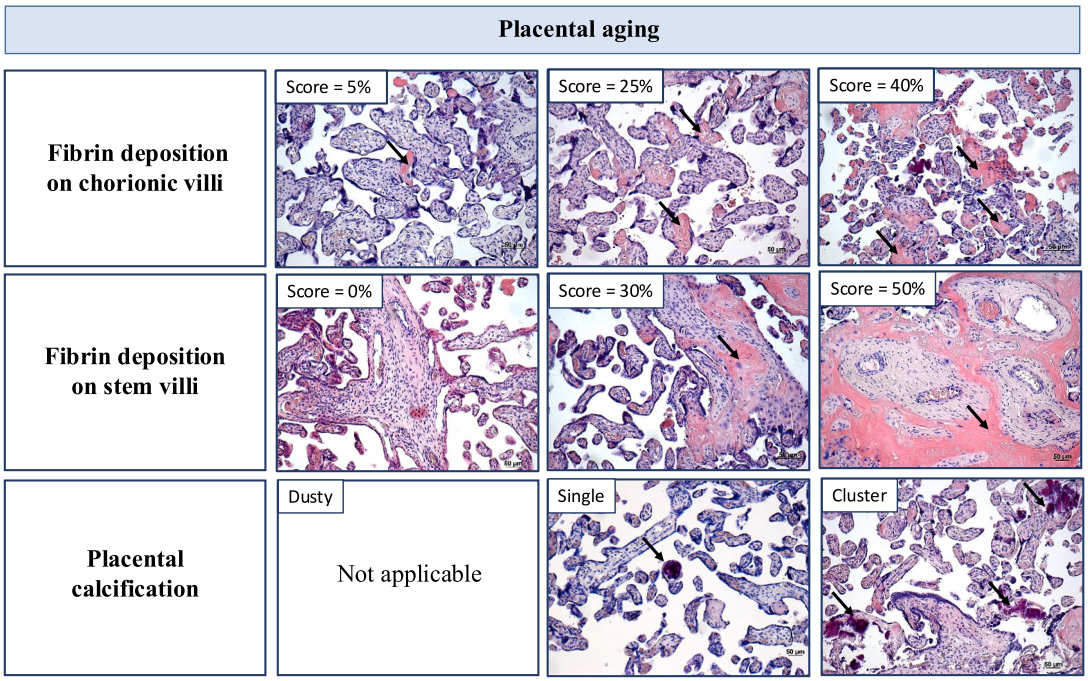

Fig. 2. Representation of the scoring method used to quantify placental parameters of aging in SEPAGES Representative photographs of the ranges of scoring used to classify the degree of placental aging. Fibrin deposition refers to accumulation of fibrin in the placenta, quantified as % and calcification refers to the pattern and grade of calcification (dichotomized using score 10 as threshold). For details on scoring of calcification, please refer to supplementary material.

PFAS in human blood (PFOS, PFOA, PFHxS, PFNA), along with structurally similar perfluoroalkyl carboxylic acids and sulfonic acids, as well as emerging PFAS with limited existing data.

Briefly, sample extracts were prepared by transferring 150 μL (Haug et al., 2009) or 50 μL (Poothong et al., 2017) of serum to a centrifugation tube, adding internal standards and methanol for precipitation of proteins, and then mixed using a whirl mixer. The samples were then centrifuged, and the supernatant was transferred to an autosampler vial, added water and mixed on a whirl mixer. Determinations were then performed using Online solid-phase extraction online solid-phase extraction with high-performance liquid chromatography and mass spectrometry (HPLC-MS-MS). To ensure that the laboratory equipment and chemicals used did not contain any traces of PFAS, procedural blanks were prepared by adding purified water to sample containers and preparing these in an identical manner as the serum samples. The quality of the determinations was also assured by analyzing in-house control samples as well as samples from a former interlaboratory comparison along with the samples. The relative standard deviations in the in-house controls were below 13 % and the mean accuracy from analyses of former interlaboratory comparison samples ranged between −12 % and 16 %.

Out of the 26 PFAS analyzed, 13 were either not quantified or quantified in less than 5 % of the samples, leading to their exclusion from further analyses (Supplementary Material, Table S3). This aligns with findings from other studies, which either did not detect these compounds or observed them in very low concentrations (Impinen et al., 2018; Miaz et al., 2020; Okada et al., 2014; Yeung et al., 2013).

2.4. Statistical analysis

2.4.1. PFAS concentration

PFAS quantified in fewer than 70 % of the samples were dichotomized (< vs. ≥ limit of quantification (LOQ)). PFAS quantified in more than 70 % of the samples were analyzed as continuous variables, with values below the LOQ being imputed using the compound's probability distribution (Helsel, 2012). Continuous PFAS were ln-transformed. Detection and quantification frequencies were calculated for PFAS concentrations. Median values and percentiles were reported for PFAS concentrations and each outcome. Spearman correlations between PFAS concentrations and between placental outcomes were also computed.

2.4.2. Adjusted association between PFAS and placental parameters

Covariates were selected a priori based on a Directed Acyclic Graph (DAG, Supplementary Material, Fig. S1). We adjusted for potential confounders (those a priori influencing both exposures and outcomes) and outcome predictors not necessarily predictors of exposures, specifically: parity (nulliparous / parous), maternal age at conception (continuous), maternal education level (<5 years after high school / 5 years or more), maternal active (no / yes) and passive (exposed to less than 1 cigarette per week / exposed to one cigarette per week or more), smoking during any trimester of pregnancy, maternal pre-pregnancy body mass index (BMI, continuous), gestational age at birth (continuous), infant's sex (female /male), maternity ward (4 categories). We additionally adjusted for some diet variables since they have been associated with PFAS exposure (Jovanovic et al. Env Int. Submitted), and may affect placental development. These included consumption of red meat (low/ moderate /high), liver (no/yes), crustaceans (never, <1/month, ≥1/month), and eggs (weekly/monthly). Missing values for covariates were < 10 % (Table 1) and were singly imputed using the median for continuous variables or the mode for categorical variables.

2.4.2.1. Single chemical analyses. Adjusted linear regression models were used for all outcomes except the dichotomized calcification score, for which we used adjusted logistic regression models. Only continuous PFAS variables were included in the logistic regression model due to the limited number of women with high calcification scores and detectable levels of dichotomized PFAS.

Since PFAS exposure showed sex-specific effects in animal studies (reviewed in Supplementary Material, Table S1), we ran additional models with an interaction term between PFAS and child sex. A p-value of interaction < 0.1 was considered indicative of effect measure modification, prompting further sex-stratified analyses. Given our limited sample size, these stratified analyses were conducted only for

Table 1
Characteristics of the study populations.

Characteristic	Placental Weight Group **N = 340**[1]	Placental Histology Group **N = 367**[1]
Maternal age at conception (years)	32.3 (30.0, 35.1)	32.3 (30.0, 35.2)
Pre-pregnancy BMI (kg/m2)	21.3(19.7, 23.9)	21.2 (19.6, 23.8)
Missing	3 (0.8 %)	4 (1.1 %)
Gestational age at birth (weeks)	40 (39.1, 40.7)	40 (39.1, 40.7)
Gestational age at blood sampling (weeks)	19.4 (18, 22)	19.3 (18, 20.9)
Maternal Parity		
Nulliparous	153 (45 %)	162 (44 %)
Parous	187 (55 %)	205 (56 %)
Child sex		
Male	180 (53 %)	194 (53 %)
Female	160 (47 %)	173 (47 %)
Maternal Education		
<5 years after high school	148 (43.5 %)	157 (42.8 %)
5 years or more	190 (56 %)	208 (57 %)
Missing	2 (0.6 %)	2 (0.5 %)
Maternal active smoking during any trimester of pregnancy		
No	286 (84.1 %)	313 (93.0 %)
Yes	24 (7.7 %)	22 (6.6 %)
Missing	30 (8.8 %)	32 (8.7 %)
Maternal passive smoking during any trimester of pregnancy		
No	258 (81 %)	279 (81 %)
Yes	62 (19 %)	67 (19 %)
Missing	20 (5.8 %)	21 (5.7 %)
Maternity Ward		
1: Hôpital Couple-Enfant	103 (30.2 %)	104 (28 %)
2: Clinique Mutualiste	129 (38 %)	143 (39 %)
3: Clinique Belledone	85 (25 %)	91 (25 %)
4: Clinique des Cèdres	22 (6.5 %)	23 (6.3 %)
Other	1 (0.3 %)	4 (1.1 %)
Missing	0	2 (0.5 %)
Red Meat Consumption		
Low	105 (31 %)	117 (32 %)
Moderate	120 (35 %)	130 (35 %)
High	115 (34 %)	120 (33 %)
Liver Consumption		
Yes	75 (24 %)	78 (23 %)
No	238 (70 %)	259 (71 %)
Missing	27 (7.9 %)	30 (8.2 %)
Egg Consumption		
Monthly consumption	185 (59 %)	194 (58 %)
Weekly consumption	128 (41 %)	143 (42 %)
Missing	27 (7.9 %)	30 (8.2 %)
Crustaceans consumption		
Never	131 (42 %)	143 (43 %)
<1/month	123 (39 %)	130 (39 %)
≥1/month	58 (19 %)	63 (19 %)
Missing	28 (8.2 %)	31 (8.4 %)

[1] Median (25%, 50%, 75%) or n (%)

continuous PFAS and continuous outcomes.

2.4.2.2. Mixture models. Due to the low number of placentas with a pathological calcification score, mixture models were applied exclusively to continuous placental outcomes. Two complementary approaches were used to investigate the mixture effect of PFAS.

PFAS Cluster Analysis: In a previous analysis of SEPAGES cohort, a cluster analysis via the VarSelLCM package in R (Marbac and Sedki, 2017) identified three PFAS exposure groups (Supplementary Material, Fig. S2), characterized by lower, moderate and higher pregnancy PFAS (PFNA, PFOS, PFUnDA, PFDA, and PFHpS) concentrations (Marbac and Sedki, 2017; Philippat et al., 2023). Due to the small sample sizes in the group with the highest concentration (N = 37 for histological parameters and N = 35 for placental weight), the moderate and higher exposure groups were combined. This two categories cluster variable was then regressed against all placental outcomes (except calcification) using the lower exposure group as reference and adjusting for covariates.

Adjusted Bayesian Kernel Model Regression (BMKR): BMKR model (Bobb et al., 2015) was used to evaluate the impact of continuous PFAS chemical mixtures on all placental outcomes (except calcification). Each model underwent 50,000 iterations, plotting the change in placental outcomes with increasing quantiles of PFAS exposure, compared to their fixed values at the 10th percentile.

2.4.3. Sensitivity analysis (applied to the uni-pollutant models)

We performed several sentivity analyses applied to the uni-pollutant models:

1. To evaluate if the associations between continuous PFAS and placental outcomes were monotonic, we categorized PFAS concentrations into tertiles and included these categories in our adjusted regression models. Due to the low number of calcification cases, we excluded this outcome. Heterogeneity across tertiles was assessed with Wald's test, and p-trend was estimated by using categorical variables whose values corresponded to the tertile-specific medians (Philippat et al., 2012).
2. Since some of the continuous outcomes (capillary density, reduced intervillous space, villi with syncytial knots and fibrin deposition) were percentages with non-normal distribution, we also applied a beta regression model (Ferrari and Cribari-Neto, 2004).

3. To mitigate the potential impact of extreme values, we applied the winsorization method. Data points below the 1st percentile and above the 99th percentile for continuous PFAS concentrations and outcomes were replaced with the respective values of the 1st and 99th percentiles.
4. Since gestational age at birth may lie on the causal pathway between PFAS and outcomes (Supplementary Material, Fig. S1), we excluded it as a covariate from the models.
5. To investigate potential selection bias, we applied inverse probability weighting (IPW) (Hernán and Robins, 2020) for analyses of placental weight and PFR, which had the largest proportions of missing values. Each participant was assigned a weight equal to the inverse of the probability of having a recorded placental weight. This probability was derived from a logistic regression model including the main covariates and mode of delivery, a key predictor of placental weight missingness (Supplementary Material, Table S4). Weights were then used in uni-pollutant models.

2.4.4. Interpretation of the results

We set the significance threshold at a p-value of < 0.05. However, results were not interpreted solely on statistical significance and p-values between 0.05 and 0.10 were considered as suggestive of an association, if it followed a pattern of associations (i.e., the considered PFAS tended to be associated with several placental outcomes)

2.4.5. Software

Analyses were performed with R 4.3.2. Data is available upon reasonable request to the SEPAGES steering committee.

3. Results

3.1. Population characteristics

Among the 484 pregnant women, 340 had data on both PFAS and placental weight, while 367 had data on PFAS and histological parameters, as shown in Supplementary Material, Fig. S3. Women were 32.3 years old at enrollment (median), with a majority being multiparous (56

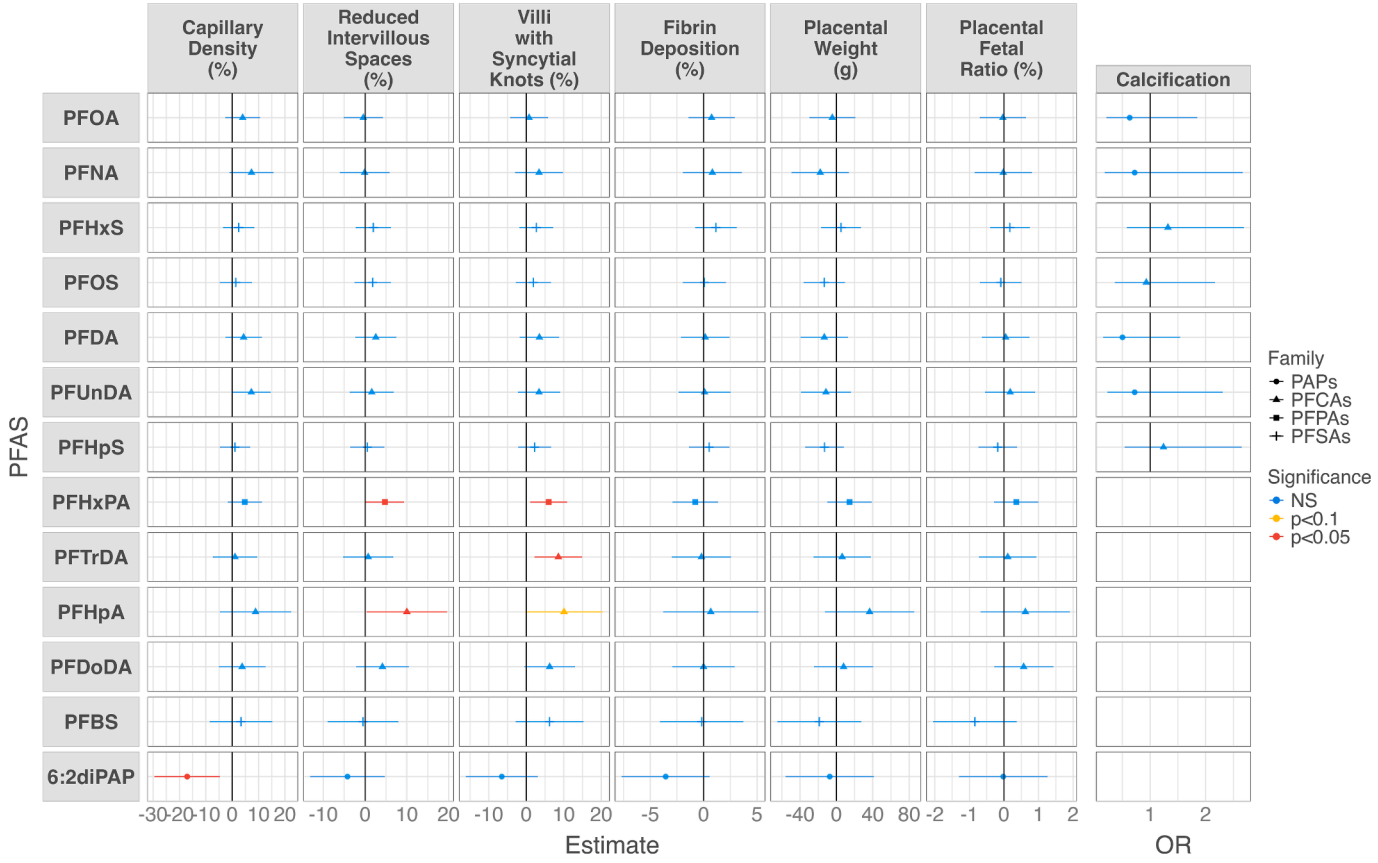

Fig. 3. Adjusted associations between individual PFAS and Placental Parameters (uni-pollutant models) Adjustment factors: Maternal age, parity, education level, active smoking, passive smoking, BMI before pregnancy, gestational age, infant sex, maternity ward, consumption of the following: red meat, eggs, liver and crustaceans. Significant $p \leq 0.05$, Trend $p \leq 0.1$. N for histological parameters = 367, Placental weight and PFR = 340 and for Calcification = 319. Capillary density refers to the density or quantity of the microvascular fetal capillary networks within the mature intermediate villi, quantified as %. Reduced Intervillous Space refers to percentage of closure of the intervillous space, quantified as % and serves as an indicator of fetal maternal exchange dynamics. Villi with syncytial knots refers to percentage of villi with trophoblastic nuclear clusters. Fibrin deposition refers to accumulation of fibrin in the placenta, quantified as %. Abbreviations: OR = odds ratio, PFAS: poly- and perfluoroalkyl substances diester, PFOA: Perfluorooctanoic acid, PFNA: Perfluorononaoic acid, PFHxS: Perfluotohexane sulfonic acid, PFOS: Perfluorooctanesulfonic acid, PFDA: Perfluorodecanoic acid, PFUnDA: Perfluoroundecanoic acid, PFHpS: Perfluoroheptanesulfonic acid, PFHxPA: Perfluorohexylphosphonic acid, PFTrDA: Perfluorotridecanoic acid, PFHpA: Perfluoroheptanoic acid, PFDoDA: Perfluorododecanoic acid, PFBS: Perfluorobutanesulfonic acid, 6:2diPAP: 6:2 Fluorotelomer phosphate. PCA-Perfluoroalkyl carboxylic acids, which includes PFOA, PFNA, PFDA, PFUnDA, PFDoDa, PFHpA, PFTrDa. PFSA-Perfluoroalkane sulfonic acids, which include PFHxS, PFOS, PFHpS, PFBS. PFPA-Perfluoroalkyl phosphonic acids, which includes PFHxPA. PAP- n:2 polyfluoroalkyl phosphoric acid esters which includes 6:2diPAP. Log transformed PFAS: PFNA, PFOS, PFOA, PFHxS, PFDA, PFHpS, PFUnDA. Corresponding effect estimates and 95 % CI for main model provided in Supplementary Material, Table S7. For Calcification, only continuous PFAS used in this analysis due to the limited number of women with high calcification scores and detectable levels of dichotomized PFAS. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

%) and delivering at 40 GW (median). Most participants (57 %) had completed five or more years beyond high school (Table 1).

3.2. Concentrations of PFAS

The quantification frequencies of PFAS showed considerable variability. Notably, quantification frequencies for six PFAS (PFOA, PFNA, PFHxS, PFOS, PFDA, and PFUnDA) were above 97 %, while PFHpS had a slightly lower quantification frequency at 84 %. Quantification frequencies for other PFAS ranged from 6 % to 52 % (Supplementary Material, Table S5).

PFHpS showed a moderate correlation with PFOS (Spearman correlation coefficient (rho) = 0.77) and PFHxS (rho = 0.78), while PFNA was moderately correlated with PFOS (rho = 0.72) and PFDA (rho = 0.76). PFDA was also correlated with PFUnDA (rho = 0.72). Correlations between the other PFAS were generally low, with rho values between 0.22 and 0.66 (Supplementary Material, Fig. S4).

3.3. Placental outcomes

Mean placental weight was 537 g, and mean PFR was 16 %. The mean values for histological parameters of fetal maternal exchange ranged from 47 % (reduced intervillous spaces) to 58 % (villi with syncytial knots, Supplementary Material, Table S6). The Spearman correlation analysis indicated a moderate correlation between placental weight and PFR (rho = 0.74) and a low correlation between histological parameters (rho values between −0.18 and 0.39, Supplementary Material, Fig. S5).

3.4. Associations between individual PFAS and placental parameters

Some categorical PFAS (PFHxPA, PFHpA) showed association with multiple histological parameters (Fig. 3 and Table S7). Women with quantified PFHxPA (N = 190) had higher percentages of villi with syncytial knots (β = 6.0 % [95 % CI: 1.1; 11) and of reduced intervillous space (β = 4.7 % [95 % CI: 0.1; 9.3]), than those with unquantified PFHxPA (N = 177). A similar pattern of associations, suggesting decreased fetal maternal exchange was observed for PFHpA, which also showed positive associations with both villi with syncytial knots (β = 10 % [95 % CI: −0.3; 20]) and percentages of closure of intervillous space (β = 10 % [95 % CI: 0.4; 20). We also observed an (isolated) association between PFTrDA and the percentage of villi with syncytial knots clusters (β = 8.6 % [95 % CI: 2.2; 15] among women with quantified PFTrDA (N = 72) compared to those with unquantified concentrations (N = 295). Finally, women with quantified 6:2 diPAP (N = 25) had lower capillary density (β = -17 % [95 % CI: −30; −5]) compared to those with unquantified 6:2 diPAP (N = 340). No association was observed between individual PFAS and calcification (Fig. 3 and Table S7), placental weight or PFR (Fig. 3 and Table S8).

Overall, these observed associations were not modified by child sex (Supplementary Material, Tables S7-8). The lowest p-values for interaction were noted for the association between PFOA and PFR (p = 0.10, Supplementary Material, Table S8). Sex stratification revealed no significant association in boys (β = 0.6 % [95 % CI: −0.3; 1.5]) but a trend towards a negative association in girls (β = -1.0 % [95 % CI: −2.0; 0.1]).

3.5. PFAS cluster analysis and BKMR

Our analyses evaluating the effect of mixture either using clustering or BKRM, did not indicate associations with placental parameters (Table 2 for the cluster analysis and Supplementary Material – Fig. S6 for BKMR). The only exception was observed in the PFAS cluster analysis, which suggested a decreased placental weight (β = -30 g [95 % CI: −56; −4] among women in the moderate-to-higher PFAS exposure cluster (N = 220), compared to those in the lower exposure cluster (N = 120, Table 2). However, it is important to note that the PFAS showing deleterious associations in the uni-polluants models were not included in these mixture analyses.

3.6. Sensitivity analysis (uni-pollutant models)

Overall, most of the observed associations persisted across our sensitivity analyses (Supplementary Material, Fig. S7 and Tables S9-12). With a few exceptions (i.e. PFOS and closed intervillous spaces: inverted U-shaped, PFUnDA and capillary abundance: U shaped), our tertile analysis did not highlight non-monotonic association (Supplementary Material, Tables S13, S14).

4. Discussion

We observed deleterious associations between three PFAS (PFHxPA, PFHpA, and PFTrDA) and the percentages of reduced intervillous spaces and villi with syncytial knots, suggesting impaired fetal maternal exchange. Also, 6:2 diPAP was inversely associated with capillary density, suggesting abnormal fetal vascularisation. Finally, our analysis also showed decreased placental weight in the moderate-to-higher PFAS exposure cluster. Associations were only observed with categorical exposure variables, warranting cautious interpretation of the results.

4.1. PFAS and histological markers of fetal maternal exchange

Our results suggested disruptions in fetal maternal exchanges in relation with exposure to specific PFAS, as positive associations were observed between PFTrDA, PFHxPA, and PFHpA and the percentages of villi with syncytial knots. PFHxPA and PFHpA were also associated with reduced intervillous space. Both markers are suggestive of placental

Table 2
Adjusted Association between PFAS clusters and placental histological parameters (N = 367), placental weight and PFR (N = 340).

PFAS clusters	Capillary Density (%)		Reduced Intervillous Spaces (%)		Villi with syncytial knots (%)		Fibrin Deposition (%)		Placental Weight (g)		PFR (%)	
	β	95 % CI	β	95 % CI	β	95 % CI	β	95 % CI	β	95 % CI	β	95 % CI
Low	Ref		Ref		Ref		Ref		Ref		Ref	
Moderate-high	2.3	(−4.7, 9.3)	0.8	(−4.2, 5.8)	0.7	(−4.6, 6.0)	0.5	(−1.8, 2.8)	−30	(−56, −4.3)	−0.5	(−1.2, 0.2)

n = 133 and 234 in the low and moderate/high clusters for histological parameters and n = 120 and 220 in the low and moderate/high clusters for placental weight and PFR. Capillary density refers to the density or quantity of the microvascular fetal capillary networks within the mature intermediate villi, quantified as %. Reduced Intervillous Space refers to percentage of closure of the intervillous space, quantified as % and serves as an indicator of fetal maternal exchange dynamics. Villi with syncytial knots refers to percentage of villi with trophoblastic nuclear clusters. Fibrin deposition refers to accumulation of fibrin in the placenta, quantified as %. Adjustment Factors: Maternal age, parity, education level, active smoking, passive smoking, BMI before pregnancy, gestational age, infant sex, maternity ward, consumption of the following: red meat, eggs, liver and crustaceans. Only continuous PFAS (PFNA, PFOS, PFUnDA, PFDA, PFHpS) were used to generate the clusters (Refer to figure S2 for details)
Abbreviation: PFR-Placental fetal ratio.

malperfusion, likely contributing to placental insufficiency and hypoxia (Soares et al., 2017). These conditions have been associated with hypertensive pregnancies (Burton et al., 2019), pre-eclampsia (Yu et al., 2022), maternal anemia (Kadyrov et al., 2006, 2003), and increased risk of intrauterine growth restriction (IUGR) (Burton and Jauniaux, 2018; Kingdom et al., 2000). Exposure to 6:2 diPAP was associated with reduced capillary density, potentially leading to decrease in fetal perfusion and compromised placental blood flow and fetal nourishment (Chowdhury et al., 2024; Gude et al., 2004).

No human studies have explored the impact of PFAS on placental histology, but Chowdhury et al. investigated arterial vasculature of placental fetal surface in 175 term placentae (marcoscopic analysis, (Chowdhury et al., 2024)). They observed no association with arterial branch points, representing the placental surface vascular network but reported an inverse association between PFOA and arterial mean distance end point to the perimeter of the placental foetal surface, indicating enhanced arterial expansion and improved fetal maternal exchange (Chowdhury et al., 2024). Although both studies assessed PFAS exposure during mid-gestation (median = 19 GW in SEPAGES and 21 GW in UPSIDE (Chowdhury et al., 2024)), Chowdhury et al. did not measure PFHxPA, PFTrDA, and 6:2 diPAP, three of the PFAS for which we reported associations, thus limiting comparability.

Similarly, published animal studies did not investigate the four PFAS for which we have observed associations. However, they reported associations for other PFAS (PFOA, PFOS and PFHxS) exposure with histological parameters, such as the reduction of the fetal maternal exchange zone, increased necrotic lesions, early fibrin clot formation, and placental congestion.

Taken together with our results, these suggest adverse effects of prenatal PFAS exposure on fetal maternal exchange.

4.2. Associations between PFAS and placental weight/PFR

Although no individual PFAS were associated with placental weight or PFR, our analysis relying on the PFAS cluster variable suggested that women in the moderate-to-higher PFAS exposure group had, on average, lower placental weight compared to those in the lower exposure group. Decrease in placental weight typically reflects compromised placental function (Thornburg and Marshall, 2015) and is a central component in determining neonatal vulnerability to adult-onset diseases (Thornburg and Marshall, 2015). A study in the same population (Ouidir et al., EHP, Submitted) found no association between this PFAS cluster variable and birth weight. In humans, one study with large sample size (N = 1,400), investigated effects of individual PFAS (PFOA, PFOS) and, similarly to our study, did not identify associations with placental weight (Fei et al., 2008). Two other studies reported either an inverse association between PFNA and placental weight (Chowdhury et al., 2024) or a positive association for br-PFHxS and 6:2Cl-PFESA as well as with a mixture of 12 PFAS (Gan et al., 2024), including PFOA, PFNA, PFDA, PFUnDA, PFHpS, PFOS, and PFHxS, overlapping with those assessed in our cohort. One of these study also used FPR (N = 175) and found positive associations with PFNA and PFDA (Chowdhury et al., 2024) indicating decreased efficiency (Misra et al., 2009; Myatt, 2006). In our study using PFR, we did not observe any significant associations.

Contrasting results have also been observed in animal studies; for example, Suh et al. found gestational PFOA exposure significantly reduced placental weight (Suh et al., 2011), while the opposite was also found (Blake et al., 2020). However, a consistent reduction in placental weight was seen with gestational PFOS exposure (Lee et al., 2015; Li et al., 2016), a chemical for which no association was seen in our study.

4.3. Potential biological pathways

PFAS could affect placental health and vascularization though several mechanisms. In vitro studies indeed reported PFAS ability to bind to peroxisome proliferator-activated receptors (PPARs) and alter cellular lipid pattern, which may affect weight homeostais (Gorrochategui et al., 2014). PFAS also interrupt cytotrophoblast cell proliferation and invasion (Marinello et al., 2020) as well as decrease gene expression of the PlGF angiogenic factor (Pham et al., 2020), suggesting inhibition of the angiogenic process, which may result, among other effects, in reduced capillary density, as observed with 6:2 diPAP exposure in our study.

4.4. Strengths and limitations

Our study is the first to examine the effects of PFAS exposure on human placental histology. By including histological markers of fetal maternal exchange and aging, alongside the more traditionally used placental weight and PFR, we aimed to deepen the description of PFAS impact on placental health. Most associations were seen with histological parameters, suggesting that they might be more sensitive to environmental exposures than placental weight. However, the time between placenta expulsion and weighting was not recorded and placental weighting was performed by the medical staff present in the delivery room. This introduced greater variability and measurement error compared to an ideal scenario where the same healthcare professional used a single, standardized scale.

Our study's modest sample size may have limited our ability to detect subtle associations. We estimated power for placental weight and continuous PFAS ranged between 0.40 and 0.61. This power estimation was based on a previous SEPAGES study on phthalates and placental outcomes, hypothesing that PFAS have a similar effect as MBzP (a phthalate metabolite) on placental outcomes in terms of magnitude. As this was the first study exploring associations with histological markers, we were unable to compute power estimates for these outcomes. The sample size, with only 20 women showing excessive calcification, may also explain the absence of an association with this outcome. Such a null association could also result from outcome misclassification, as pathologists typically review slides from multiple placenta sections, (usually more than five), whereas in the SEPAGES cohort, only a single sample was available.

Measuring PFAS in blood samples collected in early pregnancy limits confounding by hemodynamic changes that occur in late pregnancy (Sagiv et al., 2018). However, our study, conducted solely in the Grenoble area, may not fully represent PFAS exposure levels across France, highlighting the need for broader geographic representation in future research endeavors. Lastly, unaccounted confounding factors, such as genetic factors influencing PFAS metabolism and placental parameters, cannot be ruled out.

5. Conclusion

Our results showed that exposure to specific PFAS may affect histological markers of fetal maternal exchange, highlighting their broad physiological impacts. As the associations observed were limited to categorical PFAS, further research is needed to confirm these findings and elucidate placental mechanisms influenced by PFAS, alone or in combination with other environmental chemicals.

CRediT authorship contribution statement

Sadia Khan: Writing – original draft, Formal analysis. **Marion Ouidir:** Writing – review & editing. **Nicolas Lemaitre:** Writing – review & editing. **Nicolas Jovanovic:** Writing – review & editing. **Sam Bayat:** Writing – review & editing. **Sarah Lyon-Caen:** Writing – review & editing, Data curation. **Pascale Hoffmann:** Writing – review & editing. **Morgane Desseux:** Writing – review & editing. **Cathrine Thomsen:** Writing – review & editing, Resources. **A. Couturier-Tarrade:** Writing – review & editing, Funding acquisition. **Line Småstuen Haug:** Writing – review & editing, Resources. **Séverine Valmary-Degano:** Writing – review & editing. **Valérie Siroux:** Writing – review & editing. **Rémy**

Slama: Writing – review & editing, Resources, Funding acquisition. **Nadia Alfaidy:** Writing – review & editing, Resources, Conceptualization. **Claire Philippat:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2025.109308.

Data availability

Data will be made available on request.

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Further reading

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