



Does contaminant exposure disrupt maternal hormones deposition? A study on per- and polyfluoroalkyl substances in an Arctic seabird



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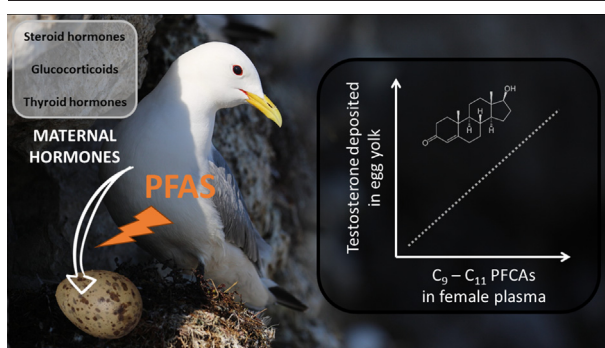
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HIGHLIGHTS

- Effects of PFAS on maternal hormone deposition were studied in Svalbard kittiwakes.
- Some hormones present in the egg yolk were compared to female plasma PFAS levels.
- Yolk hormone levels were not related to female hormone levels.
- Yolk thyroid and glucocorticoid levels were unrelated to females PFAS contamination.
- Yolk testosterone levels were positively related to some maternal long-chain PFCAs.

GRAPHICAL ABSTRACT



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ABSTRACT

Maternal effects are thought to be essential tools for females to modulate offspring development. The selective deposition of avian maternal hormones could therefore allow females to strategically adjust the phenotype of their offspring to the environmental situation encountered. However, at the time of egg formation, several contaminants are also transferred to the egg, including per- and polyfluoroalkyl substances (PFAS) which are ubiquitous organic contaminants with endocrine disrupting properties. It is, however, unknown if they can disrupt maternal hormone deposition. In this study we explored relationships between female PFAS burden and maternal deposition in the eggs of steroids (dihydrotestosterone, androstenedione and testosterone), glucocorticoids (corticosterone) and thyroid hormones (triiodothyronine and thyroxine) in a population of the Arctic-breeding black-legged kittiwake (*Rissa tridactyla*). Egg yolk hormone levels were unrelated to female hormone plasma levels. Second-laid eggs had significantly lower concentrations of androstenedione than first-laid eggs. Triiodothyronine yolk levels were decreasing with increasing egg mass but increasing with increasing females' body condition. Testosterone was the only transferred yolk hormone correlated to maternal PFAS burden: specifically, we found a positive correlation between testosterone in yolks and circulating maternal perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA) and perfluoroundecanoic acid (PFUnA) in first-laid eggs. This correlative study provides a first insight into the potential of some long-chain perfluoroalkyl acids to disrupt maternal hormones deposition in eggs and raises the question about the consequences of increased testosterone deposition on the developing embryo.

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1. Introduction

Freshly laid avian eggs contain, in addition to basic resources, substantial levels of maternal hormones (Groothuis et al., 2005; Schwabl, 1993). The amount of maternal hormones deposited in the egg yolk is known to be influenced by environmental factors (e.g., abiotic conditions (Lessells et al., 2016), food availability (Verboven et al., 2003) and social interactions (Pilz and Smith, 2004)), the offspring characteristics (e.g., sex of the embryo (Müller et al., 2002), laying date (Tomita et al., 2011), position of the egg in the laying order (Schwabl, 1993), composition of the egg (Groothuis et al., 2006)) and the state of the mother bird (Tschirren et al., 2009; e.g., her age, physical condition, past experience, genetic background) or the male quality (Rutkowska et al., 2020). Although mainly explored for steroids, experimental prenatal exposure to maternal hormones *in ovo* have shown to impact hatching date and offspring growth (von Engelhardt et al., 2006), metabolism (Tobler et al., 2007), immune system (Navara et al., 2005), sex-ratio (Rubolini et al., 2006), behavior (Possenti et al., 2018) and survival (Saino et al., 2005). Maternal hormones, in interaction with the offspring and maternal genotype, are believed to behave as messengers enabling adaptive maternal effects to prepare the offspring to prevailing environmental conditions (Mousseau and Fox, 1998; von Engelhardt and Groothuis, 2011). Independent regulation between circulating and transferred maternal hormones is an essential prerequisite for hormones to be adaptive regulators of offspring development. Although very little is known about transfer mechanisms, the literature suggests that such a separate control over deposition and response may at least be possible (Della Costa et al., 2020; Groothuis and Schwabl, 2008; Kumar et al., 2019; Okuliarova et al., 2018). Being the results of a co-evolutionary process between maternal transfer and offspring responses to these substances, such intergenerational effects may either have beneficial or even detrimental outcomes for the mother and/or the offspring (Hsu et al., 2020a; Marshall and Uller, 2007). Indeed, maternal effects may increase offspring fitness, but also reduce it to increase maternal survival in unprofitable conditions. Maternal hormones and the offspring's response should therefore match an optimal trade-off for a given situation.

In this context, any disruption to the transfer of maternal hormones may be detrimental not only to the offspring but also to the siblings and the parents (Bebbington and Groothuis, 2021; Groothuis et al., 2019). In birds, endocrine pathways are known to be affected by various environmental contaminants (e.g., trace elements, organic compounds; Metcalfe et al., 2022; Tan et al., 2009; Tyler et al., 1998). These contaminants are transferred to the yolk (Ackerman et al., 2017; Verreault et al., 2006) and may therefore potentially disrupt maternal hormone deposition. The effects of contaminants on maternal hormone deposition has nonetheless been seldom investigated: legacy persistent organic pollutants (POPs: organochlorines, brominated flame retardants) altered maternal steroids deposition in eggs of glaucous gulls (*Larus hyperboreus*; Verboven et al., 2008), but not in common terns (*Sterna hirundo*; French et al., 2001) and great tits (*Parus major*; Ruuskanen et al., 2019).

There is a clear need for further investigations on the effects of contaminants on the transfer of maternal hormones in eggs. Especially since most of the work has focussed on steroids, and not on other deposited hormones (e.g., glucocorticoids and thyroid hormones; von Engelhardt and Groothuis, 2011). More specifically, seabirds are exposed to a large variety of deleterious substances (Bianchini et al., 2022), but some of them receive little attention. Among them are per- and polyfluoroalkyl substances (PFAS), a family of synthetic compounds used as surface-active agents in a multitude of manufactured products: firefighting foams, waterproof clothing, non-stick cookware, coatings, food packaging (Buck et al., 2011). Despite the known PFAS endocrine disrupting capabilities (Chen et al., 2019; Coperchini et al., 2020; Di Nisio et al., 2020; Di Nisio et al., 2019; Jensen and Leffers, 2008; Rickard et al., 2022; Shi et al., 2019), to date our knowledge on that matter remains extremely limited in wildlife. Indeed, a few correlative studies on birds suggests that PFAS may affect concentrations of thyroid hormones, corticosterone and prolactin, potentially leading to effects on physiology, parental investment and incubation behaviors (Ask et al., 2021; Blévin et al., 2020; Mortensen et al., 2020; Nøst et al.,

2012; Sebastiano et al., 2020b; Tartu et al., 2014). The disrupting mechanisms are not well identified, but like other endocrine-disrupting compounds, PFAS may cause an alteration of the synthesis and breakdown, the release, transport and binding or elimination of endogenous hormones (Metcalfe et al., 2022). Specifically, some studies have shown that some PFAS are, for example, particularly prone to bind to hormone transport proteins (Jones et al., 2003; Kar et al., 2017; Mortensen et al., 2020). Previous investigations have shown that PFAS may exhibit a dissimilar relationship with circulating hormones than the more widely studied chlorinated POPs (Melnes et al., 2017; Tartu et al., 2014), which urge for additional studies regarding PFAS endocrine disrupting activities. PFAS can be transferred to the yolk (Bertolero et al., 2015; Gebbink and Letcher, 2012; Jouanneau et al., 2022), but their impact on maternal hormone deposition have not been investigated yet. Nonetheless, any disruption of the formation of maternal hormones or competitive binding by PFAS to transport proteins may lead to the deterioration of maternal hormones transfer and consequently to the transmission of maladaptive information to the offspring.

In this context, the aim of the present study is to investigate maternal hormone deposition in eggs of the Arctic-breeding black-legged kittiwake (*Rissa tridactyla*; hereafter "kittiwake"), known to be dietary exposed to PFAS in the wild (Blévin et al., 2017a; Jouanneau et al., 2022; Tartu et al., 2014). Specifically, we studied the relationship between female PFAS burden, and yolk maternal glucocorticoids (corticosterone), steroids (testosterone, dihydrotestosterone and androstenedione), and thyroid hormones (triiodothyronine and thyroxine), all known to be transferred to the eggs and to play a key role in embryo development (Groothuis et al., 2005; Groothuis and Schwabl, 2002, 2008; Ruuskanen et al., 2016; Sarraude et al., 2020a; Sarraude et al., 2020c). By sampling females during the pre-laying stage (i.e., during egg formation), and their eggs as soon as they were laid, we provide valuable insights into the relationship between maternal circulating and maternally deposited hormones, and shed light on the potential impacts of maternal PFAS on maternal transfer. Given the established endocrine disrupting properties of PFAS, we hypothesized a possible alteration of the maternal hormone's deposition, via a disrupted transfer of some hormones in eggs in the most PFAS-contaminated females.

2. Methods

2.1. Study area and sample collection

We carried out the field study between May and June 2019 in a kittiwake colony in Kongsfjorden, Svalbard (see Jouanneau et al., 2022 for further information on the field operations). Briefly, adults from 14 nests were captured using a noose at the end of a fishing rod, during the pre-laying period (i.e., at the time of egg formation), and immediately sampled for 2 mL of blood from the alar vein. Skull length (head + bill) was measured with an accuracy of 0.1 mm using a calliper and birds were weighted to the nearest 2 g with a Pesola spring balance. The sex of individuals were identified by molecular sexing from red blood cells following Fridolfsson and Ellegren (1999) and only females ($n = 14$) were kept for further analyses. At the end of each day, we separated plasma and red blood cells via centrifugation and kept both samples frozen ($-20\text{ }^{\circ}\text{C}$) until analyses. In this species, females usually lay a two-egg clutch (Moe et al., 2009). We monitored those nests daily and collected first- ($n = 14$) and second-laid eggs ($n = 11$) <24 h after laying. Hormones measured in freshly laid eggs, as we did in the present study, are entirely synthesized by the female before being transferred to the eggs (von Engelhardt and Groothuis, 2011). We weighted the eggs in the laboratory to the nearest 0.01 g, then separated yolk and albumen into microtubes and kept both samples frozen until analyses. Field operations were approved by the Governor of Svalbard and by the Norwegian Animal Research Authority (NARA, permit number 19970).

2.2. Per- and polyfluoroalkyl substances analysis

We adapted a method from Powley et al. (2005), contaminants analysis method and concentrations have been extensively described in a previous

study on PFAS maternal transfer (Jouanneau et al., 2022). Only compounds detected in >70 % of the females were kept for further investigations (see supporting information (SI), Table S1 for a list of all measured compounds and detection percentages). Consequently, only the following compounds were kept for statistical analyses: perfluorohexanesulfonic acid (PFHxS), branched perfluorooctanesulfonic acid (brPFOS), linear perfluorooctanesulfonic acid (linPFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnA), perfluorododecanoic acid (PFDoA), perfluorotridecanoic acid (PFTriA) and perfluorotetradecanoic acid (PFTeA). For all included PFAS, values lower than the limit of detection (LOD) were set to half of the LOD of the specific compound. We provided all concentrations in ng g^{-1} wet weight (ww).

2.3. Hormone analyses

We measured the following steroid and thyroid hormones in female plasma and egg yolk: dihydrotestosterone (DHT), androstenedione (AND), testosterone (T), corticosterone (CORT), triiodothyronine (T_3) and thyroxine (T_4). Extraction of the plasma and yolk samples is detailed for all hormones in the SI.

2.3.1. Steroid hormones (DHT, AND, T and CORT)

The four hormones were assayed with similar procedures: Radioimmunoassay (RIA) or Enzyme Linked ImmunoSorbent Assay (ELISA) methods. CORT and T were measured with RIA method, 100 μL of extract were incubated overnight at 4 °C with 4000 cpm of the appropriate H^3 -steroid (Perkin Elmer, US) and polyclonal antiserum (Ab). Anti-testosterone Ab was provided by Dr. Picaper (Nuclear medicine, CHU La Source, Orléans, France). The two anti-corticosterone Ab (one for plasma and one for yolk) were supplied by Merck, Sigma Aldrich, France. The bound fraction was then separated from the free fraction by addition of dextran-coated charcoal and the activity was counted on a Tri-Carb 2810TR scintillation counter (Perkin Elmer, US). AND and DHT were assayed with commercial ELISA kits supplied by IBL International (AND and DHT in yolk, ref. DB 52161 and DB 52021, respectively), Abnova (AND in plasma, ref. KA 1898) and Demeditec (DHT in plasma, ref. DE 2330).

2.3.2. Thyroid hormones (T_3 and T_4)

Total T_3 and T_4 were measured with RIA method, 25 μL of yolk extract or plasma were incubated overnight at 4 °C with 10,000 cpm of the appropriate I^{125} -steroid (Perkin Elmer, US) and polyclonal rabbit antiserum (Sigma Aldrich, France). The bound fraction was then separated from free fraction by addition of a polyclonal sheep antiserum against rabbit antiserum and the activity was counted on a Gamma Wizard 2470 counter (Perkin Elmer, US). We also calculated the T_3/T_4 ratio, often used when investigating thyroid hormones.

2.3.3. Quality control

We previously validated RIA and ELISA hormones assays on the kittiwake plasma and yolk. We diluted all extracts in the appropriate assay buffer, their displacement regression lines were all parallel to the standard ones. To guarantee the quality and control for reproducibility and precision of the RIA, hormone standards, blanks, total activity and non-specific activity were concurrently analysed. We ran all samples in duplicate in one or two runs. Additional information on the hormone analyses quality control can be found in SI, minimal detectable and intra-assay variation for plasma and yolk can be found in SI, Table S2. Samples below the LOD ($n = 6$) were replaced with a value equal to half of the LOD of the specific hormone. We provided all plasma concentrations in ng mL^{-1} , and yolk concentrations in ng g^{-1} ww. Bleeding time was kept as short as possible (mean \pm SD: 02 min 09 s \pm 36 s) and was not related to baseline CORT levels in plasma (linear model: $F_{1, 12} = 0.15, p = 0.70$).

2.4. Statistical analyses

2.4.1. Preliminary analyses

All statistical analyses were performed using R (v. 4.0.0; R Core Team, 2020). We tested the normality of residuals and visually inspected diagnostic plots for each models, to check whether the data met the linear model assumptions (Zuur et al., 2009). First, we investigated the relationship between each hormone or PFAS in females' plasma and the sampling date using linear models (LMs). If the relationship was significant ($p < 0.05$) we used the residuals of the LM instead of the specific hormone or PFAS in the following analyses. This enabled us to obtain comparable individuals by minimizing the variance due to the sampling time. T_3 and PFTeA were significantly decreasing with time in females (LM: $F_{1, 12} = 7.06, p = 0.02$ and $F_{1, 12} = 6.56, p = 0.03$ respectively) and residuals of the LM were consequently used in subsequent analyses.

2.4.2. Factors influencing the maternal transfer of hormones

We used linear mixed-effect models (LMMs, package "nlme"; Pinheiro et al., 2017) to investigate the effect of female and egg characteristics on the concentrations of each transferred hormone independently (i.e., one model per hormone). The full models included the maternal circulating concentration for the specific hormone, the female's scaled mass index (a proxy of the body condition of the female calculated following Peig and Green (2009)), the egg mass (used as a proxy of egg quality), the rank of the egg in the clutch by laying order (egg rank: 1 or 2) and the laying date of the first-laid eggs as fixed factors (see models formula in the SI). For all full LMMs, we built a set of models ranging from the full to the null model with all possible combination of predictors and we selected the best model according to the Akaike's Information Criterion for small sample size (AICc; i.e., the most parsimonious one among those with a $\Delta\text{AICc} < 2$; package "AICcmodavg"; Mazerolle, 2017). In all LMMs, the nest ID was used as a random variable to account for the relation between both eggs of a clutch and therefore avoid pseudo-replication.

2.4.3. Relationship between PFAS concentration in females and the maternal hormones in their eggs

We assessed the effect of each maternal circulating PFAS on the transfer of each maternal hormone in eggs using LMs. As females were sampled before they laid their first egg, and since females may excrete a significant amount of PFAS during the laying process, we only included first-laid eggs in these analyses to avoid biased results. We built one model per hormone. For each PFAS independently, the full model included the specific PFAS as fixed factor as well as any variables identified as having a significant impact on the specific maternal hormone concentrations in the yolk in Section 2.4.2 (except "egg rank" since only first-laid eggs were used here; see models formula in the SI). AICc selection was also performed on the full models, although only two models were compared: the full model and the full model without the PFAS variable.

3. Results

We provide the descriptive statistics for hormone concentration in females' plasma and egg yolk as well as PFAS concentrations in females' plasma in Tables 1 & 2.

3.1. Factors influencing the maternal transfer of hormones

Egg yolk hormone levels were unrelated to female hormone plasma levels (SI Table S3). First-laid eggs had significantly lower AND concentrations than second-laid eggs (SI Table S3 & Table S4; mean of first- and second-laid eggs respectively: 855 and 1030 ng g^{-1} ; confidence interval (CI) of the difference: [93.1 – 218]). We also found decreasing T_3 and T_3/T_4 ratio with egg mass (CI of the slope: [–0.021 – –0.001] and [–0.282 – –0.079] respectively; SI Table S4 & Fig. 1), but increasing T_3 and T_3/T_4 ratio with female's scaled mass index (CI of the slope: [0.000 – 0.002] and [0.001 – 0.019] respectively; SI Table S4 & Fig. 1). No other

Table 1

Descriptive statistics (mean \pm standard deviation *SD*, median and range min-max) for hormone concentrations in plasma (ng mL⁻¹) and yolk (ng g⁻¹ ww) of black-legged kittiwakes from Svalbard, samples measured below the limit of detection (LOD) included as half of the specific LOD. Dihydrotestosterone (DHT), androstenedione (AND), corticosterone (CORT), testosterone (T), triiodothyronine (T₃), thyroxine (T₄) and the ratio between T₃ and T₄ (T₃ / T₄).

	Pre-laying females			Eggs yolk		
	Mean \pm SD	Median	Min-max	Mean \pm SD	Median	Min-max
DHT	83.5 \pm 47.1	78.8	<LOD - 200	2649 \pm 856	2603	1419 - 4317
AND	0.21 \pm 0.17	0.16	<LOD - 0.53	932 \pm 219	920	573 - 1523
T	0.52 \pm 0.43	0.33	<LOD - 1.46	16.2 \pm 4.72	15.9	9.59 - 28.8
CORT	11.2 \pm 7.68	7.66	4.43 - 29.0	5.37 \pm 1.34	5.15	3.16 - 8.42
T ₃	1.04 \pm 0.58	1.17	0.17 - 1.87	0.39 \pm 0.10	0.36	0.23 - 0.63
T ₄	47.6 \pm 13.8	45.1	26.8 - 78.7	10.8 \pm 2.04	10.4	7.59 - 15.5
T ₃ /T ₄	2.21 \pm 1.33	2.14	0.48 - 4.85	3.78 \pm 1.15	3.47	2.16 - 5.93

Table 2

Descriptive statistics (mean \pm standard deviation *SD*, median and range min-max) for selected PFAS concentrations (ng g⁻¹ ww) in plasma of female black-legged kittiwakes from Svalbard (see SI Table S1 for details on the compound selection). In bold, the compounds associated with maternal T in eggs yolk.

	Mean \pm SD	Median	Min-max
PFHxS	0.23 \pm 0.09	0.21	0.11 - 0.40
brPFOS	0.75 \pm 0.49	0.86	0.03 - 1.38
linPFOS	10.8 \pm 4.70	11.3	3.14 - 17.42
PFOA	0.17 \pm 0.13	0.14	0.04 - 0.57
PFNA	1.06 \pm 0.61	1.07	0.19 - 2.44
PFDCa	1.71 \pm 1.56	1.56	0.40 - 3.26
PFUnA	6.88 \pm 3.22	7.42	1.40 - 12.4
PFDoA	1.78 \pm 0.98	1.78	0.02 - 3.76
PFTriA	7.80 \pm 3.35	7.93	1.81 - 13.9
PFTeA	1.44 \pm 0.60	1.53	0.471 - 2.63

investigated egg or female characteristics affected maternal hormones deposition (SI Table S4).

3.2. Female PFAS contamination and maternal hormone deposition

Yolk concentration of CORT, AND, DHT, T₃ and T₄, as well as T₃/T₄ ratios were not related to maternal PFAS burden in first-laid eggs (SI Table S5). The model selection showed that T was the only maternally transferred hormone related to certain female PFAS, PFNA, PFDcA and PFUnA (SI Table S5). Specifically, we found increasing T in eggs with increasing plasma circulating maternal concentrations of these three compounds with comparable strength even with different range of concentration found (PFNA: $F_{1, 12} = 5.88$; $p = 0.032$; CI of the slope: [0.41 - 7.75], PFDcA: $F_{1, 12} = 5.87$; $p = 0.032$; CI of the slope: [0.28 - 5.27], and PFUnA: $F_{1, 12} = 6.27$; $p = 0.028$; CI of the slope: [0.10 - 1.47]; SI Table S6 and Fig. 2).

4. Discussion

We investigated maternally deposited concentrations of androgens, glucocorticoids and thyroid hormones in egg yolk of black-legged kittiwake in relation with the female's and eggs characteristics, and the potential disrupting effect of PFAS on maternal hormone deposition. We found that egg yolk hormone levels were unrelated to female hormone plasma levels at the time of sampling, but that laying order, egg mass and the female's scaled mass index appeared to influence yolk concentration of some of the studied hormones. We observed an increased maternal T deposition in the first-laid egg in females bearing high levels of PFNA, PFDcA or PFUnA.

4.1. Factors influencing the maternal transfer of hormones

Differential deposition of androgens along the laying sequence – as observed for AND in the present study – has been described as a mean to influence the outcome of sibling rivalry in various avian species implementing brood reduction, ultimately maximising females' reproductive

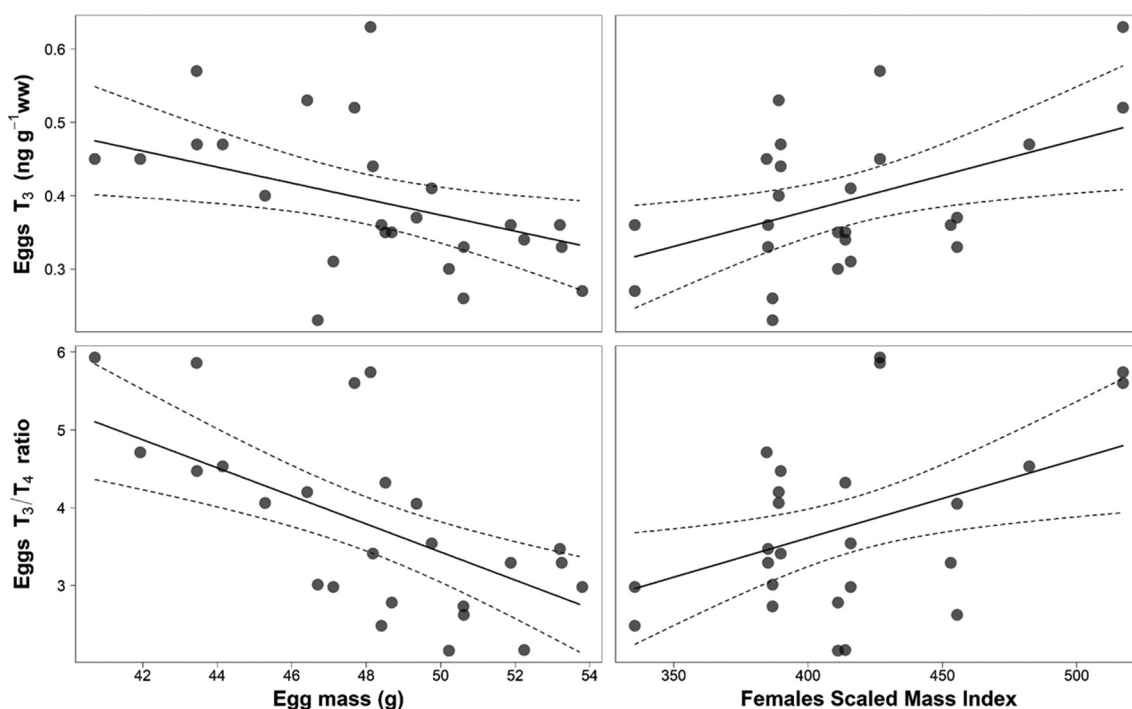


Fig. 1. Yolk maternal hormone concentrations relationship with total egg mass, in eggs of black-legged kittiwake from Svalbard for triiodothyronine (T₃) and the ratio triiodothyronine/thyroxine (T₃/T₄). The solid line refers to a statistically significant relationship (see SI Table S4), with dotted lines representing 95 % confidence intervals.

outputs (Eising et al., 2001; Muriel et al., 2019; Poisbleau et al., 2011). Studies on black-legged kittiwakes have reported higher T and AND in second-laid eggs, the amount deposited likely being determined by a complex trade-off between offspring and mother fitness and the outcomes of such a differential deposition largely depends on females and environmental conditions (Benowitz-Fredericks et al., 2013; Gasparini et al., 2007; Müller et al., 2012; Vallarino et al., 2011). Higher androgen concentrations enhance embryo growth and therefore reduce the detrimental effect of hatching asynchrony for the junior egg, however, at the expense of potential long-term costs for the offspring (Groothuis et al., 2005). Interestingly, contrary to AND, we did not observe any difference in the deposition of T, DHT or CORT in first- and second-laid eggs in the present study, despite the fact that they are all products of the same metabolic pathway.

Recent studies showed that maternal deposited thyroid hormones were associated with environmental factors including food availability and temperature experienced during the pre-laying stage (Hsu et al., 2022; Ruuskanen and Hsu, 2018). Their effects are still unclear but seem to occur mainly during the embryological development period and largely act on offspring growth and positively impact hatching success and telomere length during early postnatal period (Hsu et al., 2019; Ruuskanen et al., 2016; Sarraude et al., 2020a; Sarraude et al., 2020b; Sarraude et al., 2020c; Stier et al., 2020). The increasing concentration of maternal T₃ (but not T₄) deposited with increasing females scaled mass index found in the present study may illustrate that females in good condition can invest more in their offspring than those in lower condition. However, heavier eggs – which have been identified in many species as eggs of higher quality, leading to a higher survival probability of the offspring (Williams, 1994) – received lower T₃ concentrations (but not T₄) than lighter eggs, although we investigated concentrations and not total deposited amount in eggs. Data on yolk thyroid hormones are very limited for birds at the moment and the factors driving thyroid hormone deposition in eggs are still unclear and need further clarifications (Hsu et al., 2020b).

Other factors including adult features (e.g., age, past experience, phenotype and genetic (Tscharren et al., 2009; von Engelhardt and Groothuis, 2011)), and the environment experienced before or during egg laying by females (e.g., food quality and availability (Gasparini et al., 2007; Verboven et al., 2003) or social interactions (Bentz et al., 2016)) were also proven important predictors of maternal hormones deposition in eggs. These data were not available in the present study and would be interesting to include in further integrative studies. That being said, breeding occurred extremely late in 2019 (laying date median in the whole colony in 2019: 25th of June, 10 days later than usual average median laying date for the same population; Keogan et al., 2022). It is likely that this late breeding was a consequence of delayed food supply which may have affected hormone levels (e.g., corticosterone; Goutte et al., 2014; Riechert et al., 2014). The maternal hormones deposition may thus have been largely impacted by these particular conditions. Therefore, we do recommend additional investigations in various environmental conditions, as well as experimental studies, to better identify the drivers of maternal hormone deposition in eggs.

4.2. Female PFAS contamination and maternal hormone deposition

Very few studies explored the relationship between endocrine-disrupting chemicals (EDCs) and maternal transferred hormones in avian or non-avian oviparous species, and to the best of our knowledge, only two studies found a correlation (Hamlin et al., 2010; Verboven et al., 2008), when others could not demonstrate any clear tendency (French et al., 2001; Johnston et al., 2005; Ruuskanen et al., 2019). Several emerging and legacy PFAS are suspected or identified EDCs (Coperchini et al., 2020; Johnson et al., 2021), and recent studies on seabirds and raptors have reported association between glucocorticoids, thyroid hormones and some long-chain perfluoroalkyl acids (Ask et al., 2021; Choy et al., 2022; Melnes et al., 2017; Sebastiano et al., 2020a; Sun et al., 2021; Tartu et al., 2014). Regarding maternal hormones transfer to the eggs, our study shows that PFNA (C₉), PFDCa (C₁₀) and PFUnA (C₁₁) concentrations in

females are positively correlated with maternal T concentration in eggs. No significant correlations could be found for the perfluoroalkyl carboxylic acids (PFCAs) with longer carbon chains (C₁₂ – C₁₄), even though they were present at comparable concentrations. Long-chain PFCAs (≥ C₉) have very similar physico-chemical characteristics (Thackray et al., 2020), we could therefore expect a similar mode of action for them, and so, an additive effect when adding up the concentrations. However, no correlation was found between the sum of long-chain PFCAs (C₈ – C₁₄) and T (LM: $F_{1, 12} = 3.24$; $p = 0.097$; CI of the slope: $[-0.05 - 0.50]$). There was also no significant relationship between maternal T deposited in eggs and females PFOS (brPFOS or linPFOS) although it is the predominant compound in females' plasma (Table 2). Perfluoroalkyl sulfonic acids (PFASs) including PFHxS and PFOS have different physicochemical properties than PFCAs. Despite high PFOS concentrations and that this compound was previously found to downregulate the production of T in humans and rats (Tarapore and Ouyang, 2021), PFOS may be less prone to affect T transfer than long-chain PFCAs. Although we cannot exclude that the observed relationships for C₉ – C₁₁ PFCAs may have been induced by unidentified, correlated factors, our results suggest that at least some long-chain PFCAs may cause a disruption of the maternal hormones concentrations in eggs.

A hypothesis behind this relationship may include disturbance of T biosynthesis or breakdown mechanisms by PFAS. Among hormones, if androgens are mainly formed in the theca interna cells of the follicles wall, thyroid hormones and corticosterone are synthesized by distant glands (thyroid and adrenal glands, respectively) of the mother bird (Groothuis and Schwabl, 2008). All hormones are then transferred to the oocyte via blood, although the mechanisms are still largely unexplored (von Engelhardt and Groothuis, 2011). For instance, a disrupting effect of PFAS on the steroidogenesis may happen as steroids are produced from cholesterol, whose concentration in blood is known to be affected by PFAS in vertebrates (Geiger et al., 2014; Geng et al., 2019; Jacobsen et al., 2018; Lin et al., 2019; Roth et al., 2021). However, we would expect a similar disruption in females' plasma, which was not the case (LM for PFNA: $F_{1, 12} = 1.79$; $p = 0.206$; CI of the slope: $[-0.67 - 0.16]$, PFDCa: $F_{1, 12} = 1.17$; $p = 0.30$; CI of the slope: $[-0.43 - 0.15]$, and PFUnA: $F_{1, 12} = 0.73$; $p = 0.41$; CI of the slope: $[-0.11 - 0.05]$). A disruption of the steroidogenesis may also happen at the enzymatic level. AND is metabolized to T by the 17 β -hydroxysteroid dehydrogenase (17 β -HSD) which is known to be inhibited by PFAS in humans and rats (Zhu et al., 2020). However, this reduced the production of T and thus cannot explain the higher levels of T observed in eggs of females with higher PFAS concentration. Another hypothesis could involve gonadotrophic hormones such as luteinizing hormone (LH). PFAS are known to affect LH in humans (Raymer et al., 2012), but this hormone was found essential to control T deposition in Japanese quails (*Coturnix japonica*; Okuliarova et al., 2018). We did not measure LH in females and thus cannot explore this assumption, but this may be a valuable lead to explore in further studies.

Maternal hormone transfer mechanisms may also be affected. Unlike other vertebrates, birds do not produce any transport protein with high affinity to steroids as the sex hormone-binding globulin (Wingfield et al., 1984). Instead, the corticosteroid-binding globulin which has a high affinity for CORT, may also transport androgens (Lin et al., 2021; Vashchenko et al., 2016). Lipoproteins and albumin may bind to all steroids as well, with a low affinity (Malisch and Breuner, 2010; McNabb and Morgan, 1997). PFAS in blood are bound to albumin, fatty-acid binding proteins and organic anion transporters (Ng and Hungerbühler, 2014). Therefore, a competition for blood transporters, including albumin, between PFAS and maternal T during the process of maternal transfer to egg should result in a negative relationship between PFAS in females and deposited T in eggs, but we observe an opposite trend. Also, a displacement of hormones fixed to albumin by PFAS has previously been described as unlikely at environmental concentrations (Jones et al., 2003). An alternative explanation can be offered on the basis of the molecular structure of the observed PFCAs. In kittiwakes, PFAS are linearly positively correlated between females and their eggs for most compounds, with the transfer efficiency depending on their physico-chemical characteristics caused by the increasing

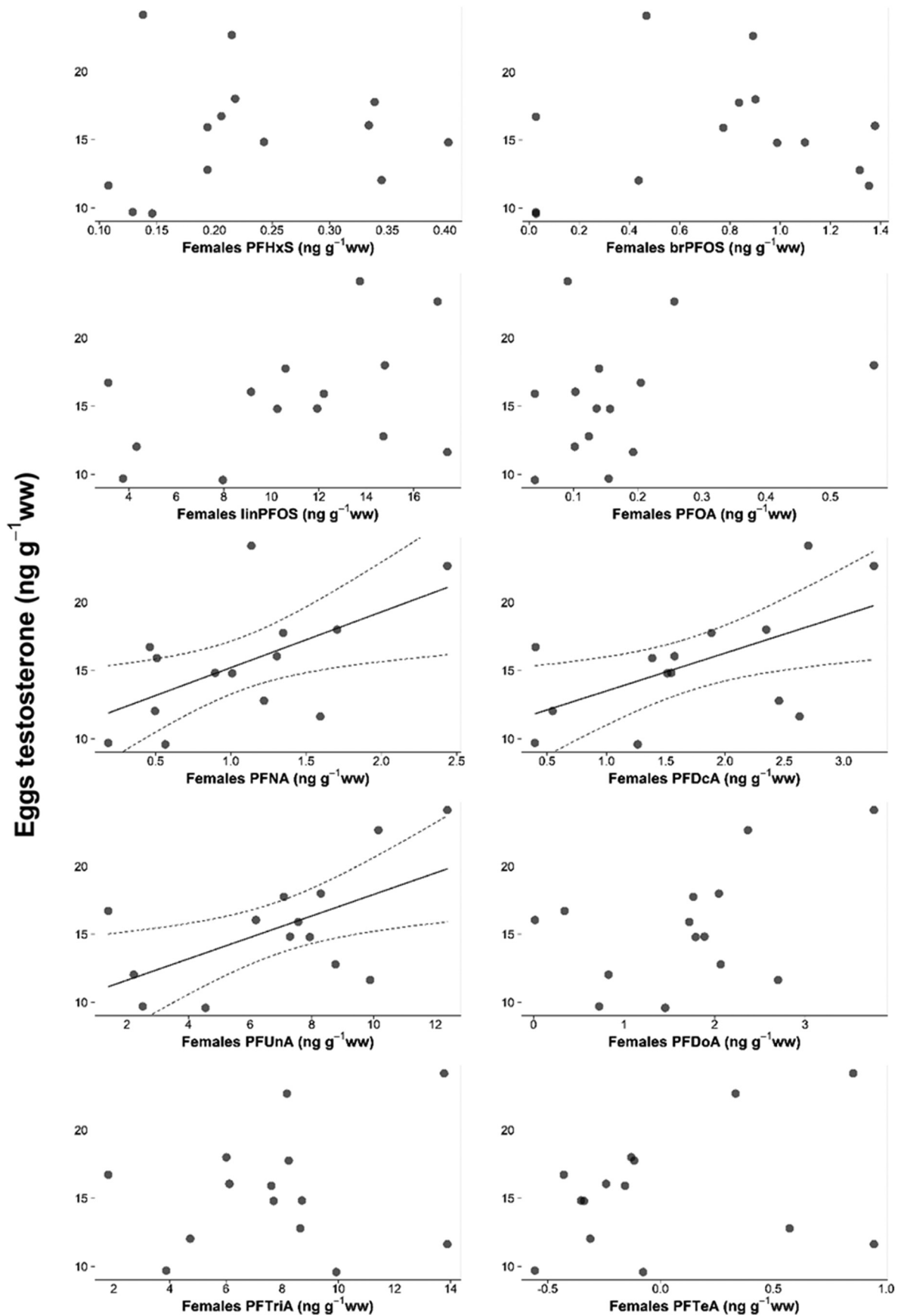


Fig. 2. Relationships between maternal testosterone concentration in first-laid eggs yolk and circulating PFAS in plasma of black-legged kittiwake females from Svalbard. The solid line refers to a statistically significant relationship (see SI Table S6), with dotted lines representing 95 % confidence intervals and no line representing no significant relationship. PFTeA in females was detrended by female sampling date (see Statistical analyses section).

perfluorinated carbon chain length (Jouanneau et al., 2022). Therefore, we can predict that the disrupting activity of PFAS in general and PFCAs with medium long chain length (C_9 – C_{11}) on T will vary according to the PFAS carbon chain length. In our study, the sample size was relatively low, which may limit the relationship between T and some of the PFAS. Further studies with a larger sample size would be essential to investigate the aforementioned hypotheses.

Overall, our study provides further evidence that certain long-chain PFCAs are the most associated with effects in this kittiwakes' population (Blévin et al., 2017a; Blévin et al., 2020; Blévin et al., 2017b; Costantini et al., 2019; Tartu et al., 2014), and that it is essential to investigate how single compounds affect physiological markers, in addition to how they act together (Sebastiano et al., 2020a). However, correlative studies in wild populations need to be interpreted with caution as the observed relationship between C_9 to C_{11} PFCAs and T may be the consequence of alternative and unknown correlated contextual cues. Maternal yolk hormone concentrations are related to egg quality in some species, therefore in this wild population, females feeding on higher trophic level could accumulate more PFAS and invest more in reproduction by laying eggs with higher T concentrations.

A large body of literature describes the consequences of high T concentrations in eggs. In semi-precocial seabirds, elevated yolk T was related to various development factors on offspring of seabirds from the same family (impaired sex-ratio (Rubolini et al., 2006), growth and body mass (Eising et al., 2001; Parolini et al., 2017; Rubolini et al., 2006), increased begging (Boncoraglio et al., 2006), competitiveness (Müller et al., 2009) and survival (Eising and Groothuis, 2003), decreased hatching time (Eising et al., 2001), immune response (Muller et al., 2005) and telomere length (Parolini et al., 2019)). In kittiwakes more specifically, experimentally elevated T in eggs led to an increased aggressiveness and dominance in the clutch (Müller et al., 2013; Müller et al., 2012). Most of the studies cited above investigate the effects of experimentally elevated T, which often exceed T concentrations observed in wild populations. Embryos *in natura* may buffer maternal T through inactivation pathways, which could at least reduce the impact of an elevated deposition of maternal T (Campbell et al., 2020). A disruption of maternal deposited T may impact the embryo at different levels, inducing a mismatch between the environment experienced early and later in life by the offspring and its phenotype, which may ultimately affect its survival and fitness. Moreover, in kittiwakes, the most PFAS contaminated females laid the most contaminated eggs (Jouanneau et al., 2022), therefore the disrupted deposition of maternal T and the high concentrations of PFAS in females and eggs may have additive consequences on the embryo (known to be particularly sensitive to EDCs; Hamlin and Guillette, 2011) through disruptions of the maternal adaptive effect, of embryo development and of the female's behavior during incubation and chick-rearing periods.

In the present study, we found no effect of PFAS on CORT and thyroid hormones (THs) deposition in eggs, despite these contaminants being known to negatively correlate with circulating CORT, and positively correlate with circulating THs in seabirds including kittiwakes and some birds of prey (Ask et al., 2021; Choy et al., 2022; Sebastiano et al., 2020b; Sun et al., 2021; Tartu et al., 2014). CORT is known to be affected by food availability (Goutte et al., 2014; Riechert et al., 2014). It is likely that the late breeding in 2019 was a consequence of delayed food supply which may have affected CORT levels. This may have, in turn, affected the maternal deposition of CORT in the yolk and possibly affected the relationship between PFAS and CORT deposition. Investigating of this relationship in different environmental contexts ("good" and "poor" conditions), may help in concluding on how PFAS may affect the maternal transfer of CORT. Concerning THs disruption by PFAS, mechanisms affected were explored in humans and birds and may include interaction with THs receptors and binding proteins, with the thyroid peroxidase enzyme activity or with thyroid-stimulating hormone (Fenton et al., 2021; Kar et al., 2017; Mortensen et al., 2020). In birds, maternal THs were found to impact several parameters in embryogenesis development and in post-hatch performance and fitness (Darras, 2019; Hsu et al., 2019; Sarraude et al., 2020a; Sarraude et al., 2020c;

Stier et al., 2020). Therefore, the impact of PFAS may be limited on these endpoints during kittiwake embryo development, at least at the concentrations we measured in the present study.

5. Conclusion

This study identified some of the main factors driving the deposition of several major maternal hormones in eggs of the black-legged kittiwake. It also produced a first insight into the relationship between females PFAS burden in plasma and maternal transferred hormones in egg yolk. None of the investigated thyroid (T_3 and T_4) and glucocorticoid (CORT) hormones deposition seemed to be affected by female contamination. Similar results were observed for steroid hormones including AND and DHT, but we observed a positive relationship between some long-chain PFAS and T deposited in eggs. Although our results do not provide evidence for a causal relationship between PFAS contamination in females and maternal T in eggs, we suggested that the transfer mechanism may be similar for some PFAS and T, which may eventually affect maternal adaptive effects driven by T deposition.

Nonetheless, maternal hormones deposition depends on a complex combination of various intrinsic and extrinsic factors, including environmental conditions. The specific context in 2019, leading to a very late breeding may thus have affected maternal hormones transfer in a specific manner. We strongly recommend additional investigations among species and time, as well as experimental studies to draw strong conclusions on the main effects of PFAS on hormone deposition in avian eggs.

CRedit authorship contribution statement

William Jouanneau: Conceptualization, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Don-Jean Léandri-Breton:** Investigation, Writing – review & editing. **Dorte Herzke:** Resources, Writing – review & editing. **Børge Moe:** Resources. **Vladimir A. Nikiforov:** Resources, Writing – review & editing. **Marie Pallud:** Resources, Writing – review & editing. **Charline Parenteau:** Resources, Writing – review & editing. **Geir W. Gabrielsen:** Investigation, Resources, Writing – review & editing, Supervision. **Olivier Chastel:** Conceptualization, Investigation, Writing – review & editing, Supervision, Funding acquisition.

Data availability

Data will be made available on request.

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.scitotenv.2023.161413>.

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