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Review article

Does variation in glucocorticoid concentrations predict fitness? A phylogenetic meta-analysis

Laura A. Schoenle[a,*], Cedric Zimmer[b], Eliot T. Miller[c], Maren N. Vitousek[b,c]

[a] Office of Undergraduate Biology, Cornell University, Ithaca, NY 14853, USA
[b] Department of Ecology and Evolutionary Biology, Cornell University, Ithaca, NY 14853, USA
[c] Cornell Lab of Ornithology, Ithaca NY 14850, USA

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ABSTRACT

Glucocorticoid hormones (GCs) are central mediators of metabolism and the response to challenges. Because circulating GC levels increase in response to challenges, within-population variation in GCs could reflect among-individual variation in condition or experience. At the same time, individual variation in GC regulation could have causal effects on energetic balance or stress coping capacity in ways that influence fitness. Although a number of studies in vertebrates have tested whether variation in GCs among individuals predicts components of fitness, it is not clear whether there are consistent patterns across taxa. Here we present the first phylogenetic meta-analysis testing whether variation in GCs is associated with survival and reproductive success across vertebrates. At the same time, we introduce and test predictions about a potentially important mediator of GC-fitness relationships: life history context. We suggest that strong context-dependence in the fitness benefit of maintaining elevated GCs could obscure consistent patterns between GCs and fitness across taxa. Meta-analyses revealed that baseline and stress-induced GCs were consistently negatively correlated with reproductive success. This relationship did not differ depending on life history context. In contrast, the relationships between GCs and survival were highly context dependent, differing according to life history strategy. Both baseline and stress-induced GCs were more strongly negatively associated with survival in longer-lived populations and species. Stress-induced GCs were also more positively associated with survival in organisms that engage in relatively more valuable reproductive attempts. Fecal GCs did not correlate with survival or reproductive success. We also found that experimental increases in GCs reduced both survival and reproductive success; however, evidence of publication bias and the small sample size suggest that more data is required to confirm this conclusion. Overall, these results support the prediction that GC-fitness relationships can be strongly context dependent, and suggest that incorporating life history may be particularly important for understanding GC-survival relationships.

1. Introduction

1.1. Glucocorticoid-fitness relationships and a role for life history

In vertebrates, glucocorticoid (GC) hormones play a critical role in mediating the phenotypic flexibility required to live in a dynamic environment (Romero and Wingfield, 2016). When an individual detects a challenge in the environment, corresponding changes in GCs enable coordinated suites of physiological and behavioral responses. GCs support responses to energetically expensive challenges that are predictable (e.g., feeding offspring: (Bonier et al., 2009b)) or unpredictable in nature (e.g., winter storms or predation risk: (Boonstra, 2013; Ramenofsky and Wingfield, 2017)), and coordinate life history trade-offs and transitions among life history stages (Crespi et al., 2013; Romero and Wingfield, 2016; Wada, 2008). These presumably adaptive functions of GCs are highly conserved across vertebrates, but maintaining high GC concentrations in order to cope with challenges can also impose costs. GCs can accelerate senescence, increase disease risk, and damage tissues, including the brain, that are integral to organismal function (Angelier et al., 2018; Haussmann and Marchetto, 2010; McEwen, 2008). Because of these trade-offs, how individuals regulate GC concentrations can influence not only their ability to navigate challenges in the short term, but also their ability to survive and reproduce. Since the 1950s, multiple hypotheses have been developed to explain how the physiological response to challenges relates to fitness (reviewed in, Schoenle et al., 2018b), and substantial empirical data has been collected from vertebrates to test these ideas.

The relationships between GCs and fitness are often predicted to

* Corresponding author at: Cornell University, 204 East Ave, 216 Stimson Hall, Office of Undergraduate Biology, Ithaca, NY 14853, USA.
E-mail address: las86@cornell.edu (L.A. Schoenle).

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Table 1
The distribution of effect sizes from observational studies included the meta-analyses by taxa, fitness measure, and GC sample type.

			Fitness Measure		Sample Type			Life History Stage of Sample Collection		
Taxa	Total Effect Sizes	Species	Survival	Reproduction	Baseline Plasma	Stress-Induced Plasma	Fecal	Breeding	Non-breeding	Year-round
Birds	88	24	22	66	60	25	3	84	4	0
Mammals	19	7	10	9	0	0	19	15	2	2
Reptiles	3	2	2	1	2	1	0	3	0	0
Fish	6	3	1	5	5	1	0	6	0	0
Total	116	36	35	81	67	27	22	108	6	2

differ under baseline and stress-induced conditions. At baseline levels, GCs bind predominantly to mineralocorticoid receptors, mediating traits related to energetic balance, including foraging behavior, body mass, and metabolism (Hau et al., 2016; Landys et al., 2006). Because GC levels increase in response to challenges, individuals with higher baseline GCs may be facing more challenging conditions, and thus, have lower fitness (reviewed in Bonier et al., 2009a). However, because GCs mediate energy use and help organisms to prepare for future challenges, higher baseline GCs could also increase reproductive success or survival under some conditions (Bonier et al., 2009a; Schoenle et al., 2018b). For example, in some avian species, higher baseline GCs are associated with greater reproductive success during the energetically expensive life history stage in which parents are feeding their offspring (Bonier et al., 2009b; Burtka et al., 2016; Henderson et al., 2017).

The rapid increase in GCs triggered by exposure to acute challenges has long been thought to promote survival over reproduction (Bókony et al., 2009; Breuner et al., 2008; Wingfield and Romero, 2001). At the time of the last comprehensive review (Breuner et al., 2008) there were few empirical tests of the relationship between stress-induced plasma GCs and either survival or reproductive success. Since that time, however, high stress-induced GC levels have been linked to lower reproductive success in a variety of species (Ouyang et al., 2012; Vitousek et al., 2014), and phylogenetic comparative studies have found that during breeding, stress-induced GC levels are lower in populations and species that engage in more valuable reproductive attempts (Bókony et al., 2009; Vitousek et al., 2019). These relationships may not, however, be ubiquitous: if mounting a strong stress response during breeding allows individuals to cope efficiently with challenges and then resume breeding activities, high stress-induced GCs could also be positively associated with reproductive success (e.g., Zimmer et al., 2019). Similarly, while the actions of glucocorticoids are consistent with promoting immediate survival, whether or not individuals with high stress-induced GCs will have higher survival is likely to depend on both the nature of the challenge(s) and their frequency or intensity (Schoenle et al., 2018b).

Although a diversity of empirical studies have confirmed that individual variation in GC regulation often predicts survival or reproductive success, previous qualitative reviews of GC-fitness relationships have found puzzlingly little evidence that these patterns are consistent across populations and species. If GCs function as highly conserved mediators of the response to challenges, why might their relationships with survival or reproduction vary? One possibility is simply that these relationships have small effect sizes or are noisy, and that insufficient data have been available – particularly for early qualitative reviews – to detect a pattern. Because GCs can mediate a diversity of different behaviors and physiological processes, variation in the exact suite of traits altered by GCs, or in the way fitness proxies are measured, could also impact the presence or detection of GC-fitness relationships (e.g., Sorenson et al., 2017). Another possibility is that the costs and benefits of having high GCs differ depending on life history – and thus, consistent GC-fitness relationships may only be apparent once life history is taken into account.

Although the relationships between hormones and fitness have long been suggested to depend on life history context (Breuner, 2010; Williams, 2012) and hormone concentrations are known to vary with life history traits (Bókony et al., 2009; Eikenaar et al., 2012; Hau et al., 2010), few empirical studies, and no large-scale comparative analyses, have tested how GC-fitness relationships among individuals vary with life history traits. Among the few empirical studies that have, the effects of GCs on survival and reproduction generally differ with life history strategy. For example, in both side blotched lizards (*Uta stansburiana*) and black-legged kittiwakes (*Rissa tridactyla*), experimental increases in GCs reduce reproduction in morphs or populations with slower paces-of-life (i.e., more K-selected strategies), but not in those with faster paces-of-life (i.e., r-selected strategies) (Lancaster et al., 2008; Schultner et al., 2013). Because of the increasing number of studies that have tested GC-fitness relationships within populations, it is now possible to use a meta-analytic approach to test whether GC-fitness relationships differ consistently across life history strategies.

1.2. Meta-analysis and predictions

Here, we use a phylogenetic meta-analysis approach to test: 1) whether GC levels are consistently related to reproductive success and survival, and 2) whether these GC-fitness relationships vary with life history. We first test the relationships between natural variation in baseline, stress-induced, and fecal measures of GCs and fitness metrics. Next, we determine whether GC manipulations have consistent impacts on survival and reproduction across species. Then, we identify how GC-fitness relationships vary with sex and two life history traits: longevity and the value of a reproductive bout. Our analyses include 116 effect sizes from birds, fish, mammals, and reptiles (Table 1) indicating that now is a critical time for such a large-scale study. However, empirical studies evaluating both fitness and GC concentrations are not equally distributed across taxa, emphasizing the importance of using phylogenetically controlled analyses to account for variation due to shared evolutionary history. Many more studies address these questions in birds, and the method of measuring GCs also varies across taxa, with plasma measures being dominant in birds, reptiles, and fish, and fecal measures being predominantly used in mammals (Table 1). We take advantage of the large number of studies addressing the relationship between natural variation in baseline GCs and reproductive success in birds (Table 1) to evaluate how GC-fitness relationships differ across two avian breeding stages: incubation of eggs and chick-rearing.

Because the benefit of elevated GCs is expected to vary across contexts, and life history can influence GC-fitness relationships, we predict that meta-analyses will show life history-dependent rather than consistent relationships between baseline GCs or fecal GCs and metrics of fitness. Similarly, we predict that analyses that do not incorporate life history will find no consistent relationship between variation in stress-induced GCs and survival; however, we predict that individuals that maintain higher stress-induced GCs during reproduction will have consistently lower reproductive success. We also include sex as a factor in our analyses, but we do not make explicit predictions for how sex should shape the GC-fitness relationship, as we predict this will be highly dependent on the breeding system.

Because GCs can affect an individual's survival over time, we predict the relationship between GC concentrations and fitness will depend on

species' longevity (Schoenle et al., 2018b). In other words, maintaining higher GC concentrations could have different fitness costs and benefits depending on lifespan. How longevity relates to GC-fitness relationships will depend on whether the costs of high GCs outweigh the benefits over time. Here we present two alternative hypotheses: 1) Elevated GC concentrations result in cumulative damage over time (McEwen and Seeman, 2004), causing longer-lived animals to suffer greater costs of high GCs than shorter-lived animals (Schoenle et al., 2018b). If this is the case, we predict that longer-lived animals will have more negative GC-fitness relationships, both in terms of survival and reproduction. 2) Elevated GCs promote survival in the face of challenges (Breuner et al., 2008; Sapolsky et al., 2000), and thus, longer-lived animals benefit more from GC-mediated increases in survival than shorter-lived animals because on average, they will have a greater number of future reproductive opportunities.

Empirical evidence exists supporting each of these hypotheses. Although we know of no studies that explicitly test relationships between GCs, tissue damage, and fitness among species varying in longevity, evidence suggests that elevated GCs can cause cumulative damage through several mechanisms. For example, GCs can cause increases in oxidative stress, altered telomere dynamics, and structural damage in the brain (Angelier et al., 2018; Costantini et al., 2011; McEwen, 2008; Sapolsky et al., 1990). In addition, GCs can increase exposure and susceptibility to parasites (Gervasi et al., 2016; Malisch et al., 2009), which can cause damage to host tissues both directly or mediated through the immune response to infection (Graham et al., 2011; Schoenle et al., 2018a). Similarly, we are unaware of studies that explicitly examine relationships between GCs, the response to challenges, and survival across species with differing lifespans. A comparative analysis in birds found that species with higher survival rates also have higher stress-induced GC concentrations (Hau et al., 2010), suggesting that elevated GCs could promote survival. However, whether or not GCs promote survival is likely to depend on the nature of the specific challenge faced, and whether GC mediated changes in physiology and behavior match that challenge (reviewed in Schoenle et al., 2018b). Thus, variation in the relationship between GCs and survival across challenge type might preclude any general patterns between longevity and the GC-survival relationship.

GCs also influence reproductive physiology and behaviors, and as a result, GC-fitness relationships are likely to be shaped by the relative value organisms place on a given reproductive bout. Species with faster pace-of-life tend to have fewer reproductive bouts and produce more offspring each bout than those with slower paces-of-life; thus, on average each reproductive attempt represents a greater proportion of total lifetime reproductive effort in these species (higher reproductive bout value: (Bókony et al., 2009; Vitousek et al., 2019)). Because acutely elevated GCs often downregulate reproduction in favor of survival, we generally predict a more negative relationship between stress-induced GCs and reproductive success when reproductive bout value is high. However, in species that engage in particularly high value reproductive attempts, selection could also favor individuals in which acutely elevated GCs do not downregulate reproduction (Boonstra and Boag, 1992; McConnachie et al., 2012). In these species, we would expect no relationship between stress-induced GCs and reproductive success. Because elevated baseline GCs may help to support periods of energetic challenge, we predict more positive baseline GC-reproductive success relationships in species with higher reproductive bout value (Bókony et al., 2009; Schoenle et al., 2017). We predict that relationships between baseline GCs and survival will not differ according to reproductive bout value.

Because of the role of baseline GCs in supporting energetically demanding periods, we predict that GC-fitness relationships will differ across life history stages (Bókony et al., 2009). In birds, we predict less negative relationships between baseline GCs and reproductive success during the offspring provisioning period than during incubation, because elevated baseline GCs could help to support this energetically demanding period (Bonier et al., 2009b).

Ideally, GC manipulations would confirm the results from studies of natural GC variation, and predictions for the relationships between experimental elevations of GCs and fitness metrics would mirror those for natural variation in GCs. However, hormone manipulations might not simply produce the same results as natural variations in concentrations of GCs. Nearly all GC-manipulation studies in wildlife use techniques such as slow-release implants, topical treatments, food supplementation, or injection to increase GC concentrations (Sopinka et al., 2015). If GC manipulations can successfully elevate GCs within the normal physiological range for a species – a common concern for such studies – most manipulations remain unable to replicate the pulsatile, cyclic release of endogenous hormones (Dantzer et al., 2016; Fusani, 2008). Therefore, experimental manipulations of GCs could influence not just hormone concentrations, but the entire HPA axis, including receptor expression and negative feedback, thus altering GC's downstream effects (Fusani, 2008). Furthermore, hormone regulation has been selected over evolutionary time, and as a result, GC manipulations that move individuals' hormone concentrations away from their natural concentrations could have negative effects on multiple aspects of fitness (Bonier and Cox, 2020; Crossin et al., 2016; Schoenle et al., 2019). Thus, we predict that experimental increases in GCs will reduce both survival and reproduction.

2. Materials and methods

2.1. Literature search

We performed a systematic review of the literature assessing the relationship between GCs and fitness metrics including both observational studies and hormone manipulation experiments. We identified relevant research by searching Web of Science using combinations of the terms "gluc*," "cort*," "fitness," "survival," and "reproduction," and searching Google Scholar (which does not allow for searching with truncations and wildcards), using many variants of the hormone names (e.g., GC, GCs, glucocorticoids, cortisol). Additionally, we searched forward and reverse citations of review and synthesis papers addressing the GC-fitness relationship including: Breuner et al., 2008; Bonier et al., 2009a; Hau et al., 2010; Sorenson et al., 2017. The search included literature published (including online publication) before January 2018.

2.2. Inclusion/exclusion criteria

We included studies that met the following inclusion/exclusion criteria: 1) Studies must have been conducted in free living vertebrates. 2) Observational studies must have measured both a fitness metric(s) and GC hormones as either baseline plasma GC concentrations, stress-induced (response to an acute stressor) plasma GC concentrations, or fecal GC metabolites. 3) Experimental hormone manipulations must have both directly altered GC concentrations by administering a hormone treatment with the goal of increasing GC levels and also assessed fitness metrics post-treatment. Studies that indirectly manipulated GCs (e.g., by food supplementation) were excluded. 4) Studies assessing survival rates must have evaluated mortality measuring return rates, resightings, or comprehensive tracking that allowed for determination of death. 5) Studies assessing reproductive success must have measured both GCs and reproductive success within the same reproductive season (i.e., not carry-over effects). 6) Measures of reproductive success must either have been the number of offspring produced or a binary, definitive evaluation of success or failure (e.g., abandoned or successfully reared offspring).

2.3. Data extraction and effect size calculations

We collected effect sizes for the relationship between GCs and

fitness metrics from reported test statistics (e.g., F, χ^2, z, R^2, r). We identified whether the fitness metric was indicative of survival or reproductive success and recorded the specific fitness measure used. For studies in which GC concentrations were manipulated, we recorded the length of time from administering the treatment until assessing the fitness metric. We also recorded the sample size, degrees of freedom (when relevant), and direction of the GC-fitness relationship. We assigned a positive value for the direction of the relationship when higher GCs were associated with higher rates of survival or reproduction and a negative value when higher GCs were linked to lower rates of survival or reproduction. For 9 effect sizes in which the GC-fitness relationship was not significant, we were unable to identify the direction of the relationship. We ran all analyses including these studies (meta-analyses for baseline GCs and experimental manipulations of GCs) by assigning all effect sizes a negative value or all a positive value (as in Bentz et al., 2016). The results of the meta-analyses did not differ qualitatively when these studies were assigned all negative or all positive values. We report the results from all analyses assuming a positive relationship. In cases where the statistics were not reported explicitly (often the case in publications using model selection as the primary analytic tool), but data were available in a repository, we used the raw data, including only GC concentrations and the focal fitness metric, to calculate the correlation coefficient r. Alternatively, if the data were not available in a repository, but were presented in a scatterplot, we used WebPlotDigitizer version 3.9 (Ankit Rohatgi, Austin, Texas, USA) to extract data and calculate r. When statistics were not reported and we were unable to access the data from a repository or graph, we contacted the corresponding author and requested data or statistics (25 effect sizes from 5 studies were obtained from author inquiries). The sources for each effect size are included in the supplementary material.

All effect sizes were converted to the correlation coefficient r using formulas from: Rosenthal and Dimatteo (2001), Nakagawa and Cuthill (2007), and Rosenberg et al. (2013). There is no widely accepted way to identify degrees of freedom from random effects models. Thus, we followed a technique used in recent meta-analyses (Bentz et al., 2016), and when calculating effect sizes from random effects models we converted the *p-value* to a normal deviate Z-score and calculated r as $r = Z/\sqrt{N}$ (Rosenthal and Dimatteo, 2001).

To avoid pseudo-replication, each effect size was assigned a reference ID and a group ID to be used as random effects in the analyses. Reference IDs were a unique number associated with each publication such that all effect sizes from a single publication were assigned the same reference ID. Group IDs indicated if the same individuals were used to calculate multiple effect sizes (e.g., the relationship was measured across multiple years or seasons using the same individuals), either within the same publication or across multiple publications.

For observational studies, we recorded whether the hormone measure was baseline, stress-induced, or from fecal metabolites based on the authors' classification of the measure. Although not included in the analyses, we also recorded the latency from capture until collecting blood to measure baseline GCs and the time after restraint at which stress-induced GCs were measured. Among studies of baseline GCs, most effect sizes were calculated using GCs measured in plasma samples collected within 3 min after capturing the animal (n = 52). However, several studies (n = 7) measured GCs over a longer time window (e.g., up to 5 min) but either verified that concentrations did not increase from baseline levels within that selected time period (e.g. Strasser and Heath, 2013) or collected most samples in less than 3 min, but the maximum latency was longer (e.g. Nelson et al., 2015). Although they met all other requirements for the analysis, we excluded 2 studies that collected blood samples 10 min after capture (Beletsky et al., 1992, 1989) and did not justify that hormone levels could be considered baseline. Latency to sample for baseline GCs was not recorded for 8 effect sizes, but studies reported collecting the samples immediately after capture (e.g. Magee et al., 2006) or using non-invasive sampling methods (Bauch et al., 2016), and these were retained in the analysis. We also recorded the length of the standardized period of restraint used prior to collecting a blood sample for stress-induced GCs. The time between stressor exposure and peak stress-induced GCs varies across species and individuals, and most species peak after 14–60 min of restraint (Breuner et al., 2008; Satterthwaite et al., 2010; Small et al., 2017). We chose to accept authors' selected timeframes as an acceptable measure for stress-induced GCs. Fecal metabolites were considered an integrative measure of hormones and were not associated with a specific time range.

For each effect size, we collected data on life history variables that could influence the direction or strength of the GC-fitness relationship. We recorded species, sex (male, female, or pooled sexes), life history stage in which the sample was collected (breeding, non-breeding, or year-round). We defined breeding as the periods of time involving preparing for breeding (e.g., mate attraction, nest building), mating, and caring for offspring shortly after birth or hatching (e.g. provisioning young in the nest (birds), lactation (mammals)). Any periods outside of this window were classified as non-breeding. We categorized studies collecting data across breeding and non-breeding stages as year-round. All studies of GC-reproductive success relationships measured GCs during breeding. We also recorded the specific sub-stage of breeding (e.g., lactation, spawning, incubation, chick-rearing). Among the included studies, non-breeding periods were distinguished from breeding periods in that they were in a spatially distinct location, did not involve parental care, or were explicitly identified by the authors as non-breeding.

We collected species- and population-level life history data to test how life history shapes GC-fitness relationships. We obtained these life history variables from the extended HormoneBase dataset (Johnson et al., 2018) including: maximum longevity, litter or clutch size, and the number of litters/clutches per year. For any species that were not in HormoneBase, we obtained these life history variables from the Amniote (Myhrvold et al., 2015) and AnAge (De Magalhaes and Costa, 2009) databases. From these variables, we calculated the expected value of a single reproductive bout (Bókony et al.'s "brood value", termed here reproductive bout value) using a version of the formula in Bókony et al. (2009): ln(clutch or litter size/[clutch or litter size × bouts per year × maximum lifespan]).

2.4. Building the phylogeny

We built a phylogeny to incorporate the evolutionary relationships among the study taxa following an identical pipeline to that described in Johnson et al., (2018). In short, we used manual taxonomic reconciliation to match every study species to a tip in a recent, large taxon-specific phylogeny: ray- finned fishes (Rabosky et al., 2013), amphibians (Eastman et al., 2013; Pyron and Wiens, 2011), mammals, squamates (Pyron et al., 2013), turtles (Jaffe et al., 2011), and birds (Jetz et al., 2012). We then pruned these taxon-specific trees to the manually matched study species, employing tip-row swaps for phylogenetically equivalent species when necessary (Pennell et al., 2016). Finally, we bound these taxon-specific trees into a backbone, vertebrate-scale phylogeny created with the TimeTree of Life (Kumar et al., 2017) such that the final tree was ultrametric and contained one tip for every species in the study.

2.5. Meta-analysis

To evaluate how GCs relate to reproductive success and survival across vertebrates, we performed eight meta-analyses of the following relationships: 1) baseline GCs and survival, 2) baseline GCs and reproduction, 3) stress-induced GCs and survival, 4) stress-induced GCs and reproduction, 5) fecal GC metabolites and survival, 6) fecal GC metabolites and reproduction, 7) experimentally manipulated GCs and survival, and 8) experimentally manipulated GCs and reproduction.

All analyses were performed in R version 3.5.1 (R Core Team, 2018)

and meta-analyses were performed using the package *metafor* (Viechtbauer, 2010). Before performing any analyses, we used the *escalc* function in metafor to convert the correlation coefficients *r* to the standardized, normally distributed effect size Fisher's Z and to calculate the sampling variance for each effect size (as described in Holtmann et al., 2016; Taff et al., 2018). Results were back-transformed to *r* to support easier interpretation.

We performed meta-analyses using linear mixed models using the *rma.mv* function in *metafor* to control for the non-independence of effect sizes collected from the same study, species, or individuals as well as non-independence associated with phylogenetic relationships. Thus, we tested for the importance of the random effects in the models following Foo et al. (2016). We tested the importance of the reference ID, species, and whenever relevant, group ID using likelihood ratio tests. We separately tested each random variable for significance within an intercept-only meta-analysis using likelihood ratio tests (see Appendix A for details). We report the retained effects in Table 3 and the statistics from each test in Appendix A.

We determined the overall effect sizes for the relationships between glucocorticoids and fitness with restricted maximum likelihood meta-analytic models including the selected random effects using the *rma.mv* function. We used a phylogenetic meta-analysis to account for the expectation of similar trait values among related species by including these relationships in the form of a phylogenetic correlation matrix random effect. For each meta-analysis, we calculated the heterogeneity statistic I^2 using the *rma.uni* function (reported in Table 3). I^2 is the percent of variability in the effect sizes (0–100%) that is due to variation in the effects (rather than sampling error) from an intercept only model with no random effects. This variation in the GC-fitness relationship might be accounted for by other moderators (e.g. sex, life history stage, breeding stage, or other factors).

2.6. Moderator analyses

To test whether GC-fitness relationships vary with context, specifically life history, we used moderator analyses to test how longevity, reproductive bout value, and sex relate to relationships between GCs and both survival and reproductive success. For the meta-analyses including baseline, stress-induced, and manipulated GCs, we tested all three moderators. We were unable to test for correlations between sex and fecal GC-fitness relationships because of a lack of effect sizes for both males and females. We conducted all moderator analyses using phylogenetically informed meta-analyses with moderators as fixed effects and the previously selected random effects using the *rma.mv* function (Viechtbauer, 2010). Because the sample size varied for different moderator analyses, we performed a separate meta-regression model for each moderator rather than including all moderators in a single analysis.

The large number of effect sizes from birds allowed us to perform additional moderator analyses to further explore the role of context in baseline GC-fitness relationships. We first performed a baseline GC-reproductive success meta-analysis using effect sizes from birds only. Of the 48 effect sizes, 40 were from distinct breeding stages: incubation and chick-rearing. Thus, following the main meta-analysis, we were able to run moderator analyses specific to birds, including not only sex, value of a reproductive bout, and longevity, but also whether the relationship between GCs and reproductive success varied across breeding stages.

We performed a moderator analysis using the effect sizes from studies manipulating GC concentrations. We tested whether or not the length of time between the hormone manipulation and when the fitness metric was assessed influenced the relationship between GCs and fitness. If the effects of GCs on fitness are limited to the short-term, then as more time passes between the treatment and assessing fitness measures the effect sizes will approach 0.

2.7. Tests for publication bias

We tested each of the eight meta-analyses for evidence of publication bias in several ways. We performed Egger's regression test (Egger et al., 1997) using the overall intercept-only models with the *regtest* function in *metafor*. Egger's test evaluates the relationship between standardized residuals and study precision. We also conducted a trim-and-fill analysis using the *trimfill* function using the L_0 estimator in *metafor* to test for asymmetry among effect sizes in a funnel plot. Funnel plot asymmetry can indicate heterogeneity among effect sizes or publication bias in favor of significant results. Finally, we used a linear regression to evaluate the relationship between publication year and effect size for time-lag bias. Evidence of time-lag bias occurs when effect sizes approach zero as time passes because studies with larger effect sizes are published faster or earlier than those with smaller effect sizes.

3. Results

3.1. GC-fitness dataset

Our dataset included 137 effect sizes from 59 publications (complete dataset provided in the supplementary material). Table 1 illustrates the distribution of effect sizes from observational studies by taxa, fitness measure, GC sample type, and the life history stage when samples were collected. Table 2 shows the distribution of effect sizes from hormone manipulation studies by taxa and fitness measure. All observational and experimental studies addressing GC-reproductive success relationships were conducted during breeding (i.e., blood sample collection and hormone manipulations were conducted during the same breeding season in that reproductive success was measured). The meta-analyses demonstrated that the relationships between GCs and fitness vary with the hormone sample type and the fitness metric used (Fig. 1). The final models for the meta-analysis, including the random effects retained, variance explained by shared evolutionary history, and I^2 (the percent of variability in effect sizes due to variation in the effects rather than sampling error), are summarized in Table 3. Details for the tests of significance of random effects are included in Appendix A.

3.2. Baseline GCs and survival

Higher baseline GCs were associated with lower survival, but the effect was small and the relationship was not significant when incorporating the expected covariance between related species due to shared evolutionary history (Fig. 1, Table 3). Moderator analyses revealed that populations and species with slower paces-of-life had more negative baseline GC-survival relationships. Longer-lived populations and species had more negative baseline GC-survival relationships than their shorter-lived counterparts ($\beta = -0.01$, 95% CI $= -0.019$ to -0.0014, $p = 0.02$, n $= 14$, Fig. 2a). Similarly, animals with a lower value for a single reproductive bout tended to show more negative baseline GC-survival relationships, but the effect was not significant ($\beta = 0.35$, 95% CI $= -0.02$ to 0.64, $p = 0.06$, n $= 14$, Fig. 2b). Sex was not associated with the baseline GC-survival relationship (males

Table 2
The distribution of effect sizes from hormone manipulation studies by taxa and fitness measure.

			Fitness Measure	
Taxa	Total Effect Sizes	Species	Survival	Reproduction
Birds	16	6	2	14
Mammals	0	0	0	0
Reptiles	3	1	3	0
Fish	2	2	1	1
Total	21	9	6	15

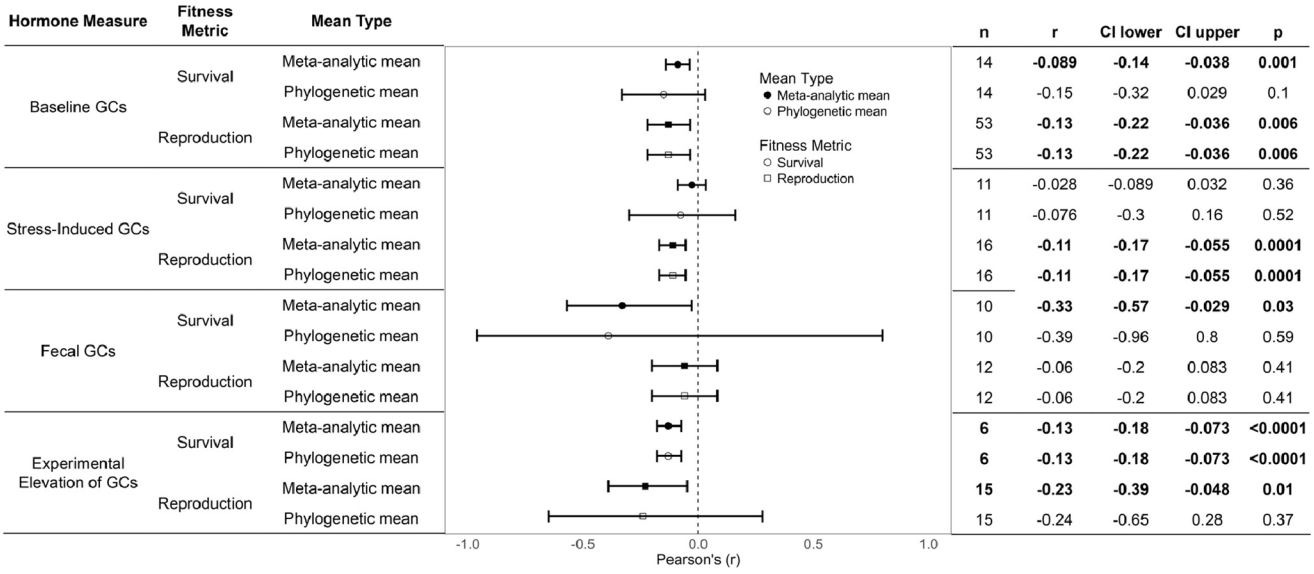

Fig. 1. Meta-analytic means and phylogenetic meta-analytic means for studies assessing the relationships between GCs and fitness measures. Means are represented as a point and error bars represent the 95% confidence interval. Significant effects are bolded.

relative to females, β = −0.043, 95% CI = −0.21 to 0.12, p = 0.61, n = 10).

3.3. Baseline GCs and reproductive success

Overall, higher baseline GC concentrations during reproduction were associated with lower reproductive success; this relationship was identical for the standard and phylogenetically-controlled meta-analyses (Fig. 1). None of the moderators accounted for the variation in the relationships between baseline GCs and reproductive success (sex (male): β = 0.076, 95% CI = −0.037 to 0.19, p = 0.19, n = 45; reproductive bout value: β = 0.057, 95% CI = −0.22 to 0.32, p = 0.69, n = 53; longevity: β = 0.0012, 95% CI = −0.15 to 0.16, p = 0.99, n = 53).

Meta-analyses within birds alone that included breeding stage as an additional moderator also revealed a significant negative relationship between baseline GCs and reproduction for both the standard and phylogenetically informed meta-analyses (for both, r = −0.12, 95% CI = −0.21 to 0.029, p = 0.01, n = 48). None of the moderators, including breeding stage, explained the heterogeneity in GC-reproduction effect sizes (sex (male): β = −0.079, 95% CI = −0.045 to 0.20, p = 0.21, n = 40; breeding stage: (chick-rearing) β = 0.12, 95% CI = −0.0044 to 0.24, p = 0.059, n = 40; longevity: β = −0.002, 95% CI = −0.012 to 0.0077, p = 0.68, n = 48; value of a reproductive bout: β = −0.05, 95% CI = −0.40 to 0.31, p = 0.79, n = 48).

3.4. Stress-induced GCs and survival

Overall, the correlation between stress-induced GCs and survival was not significant. Both the phylogenetically informed meta-analysis and the standard meta-analysis produced qualitatively similar results (Fig. 1). Relationships between stress-induced GCs and survival appeared to be strongly context dependent. Studies conducted in longer-lived animals found more negative GC-survival relationships than those conducted in shorter-lived animals (β = −0.01, 95% CI = −0.02 - −0.002, p = 0.01, n = 11, Fig. 3a). In addition, animals with a higher value for a single reproductive bout had more positive GC-survival relationships (β = 0.28, 95% CI = 0.06 – 0.48, p = 0.01, n = 11, Fig. 3b). Sex was not associated with the GC-survival relationship (males relative to females, β = 0.023, 95% CI = −0.12 to 0.16, p = 0.74, n = 8).

3.5. Stress-induced GCs and reproductive success

Both the phylogenetically informed and standard meta-analyses demonstrate a significant, negative relationship between stress-induced

Table 3
The sample size, random effects, phylogenetic variance, and I^2 for each meta-analysis.

Meta-analysis	n (Effect Sizes)	Random Effects Retained[1]	Variance (σ^2) Explained by Shared Evolutionary History[2]	I^2 (%)[3]
Baseline GCs & Survival	14	None	0.02	30.81
Baseline GCs & Reproduction	53	Group ID	0.000	79.83
Baseline GCs & Reproduction (birds only)	48	Group ID	0.000	78.91
Stress-induced GCs & Survival	11	None	0.019	57.96
Stress-induced & Reproduction	16	None	0.000	59.08
Fecal GCs & Survival	10	Reference ID	0.71	92.35
Fecal GCs & Reproduction	12	Reference ID	0.000	78.92
Experimentally Elevated GCs & Survival	6	None	0.000	75.43
Experimentally Elevated GCs & Reproduction	15	Reference ID	0.13	71.08

[1] Random effects found to be significant using likelihood ratio tests (statistics reported in the supplementary material). For each analysis we tested for the importance of reference ID (unique number associated with each publication), group ID (unique number indicating when the same individuals were used to calculate multiple effect sizes, see main text for details), and species.

[2] Variance explained by including a phylogenetic covariance matrix as a random effect in the meta-analysis.

[3] The percent of variability in effect sizes due to variation in the effects (rather than sampling error) from an intercept-only model with no random effects.

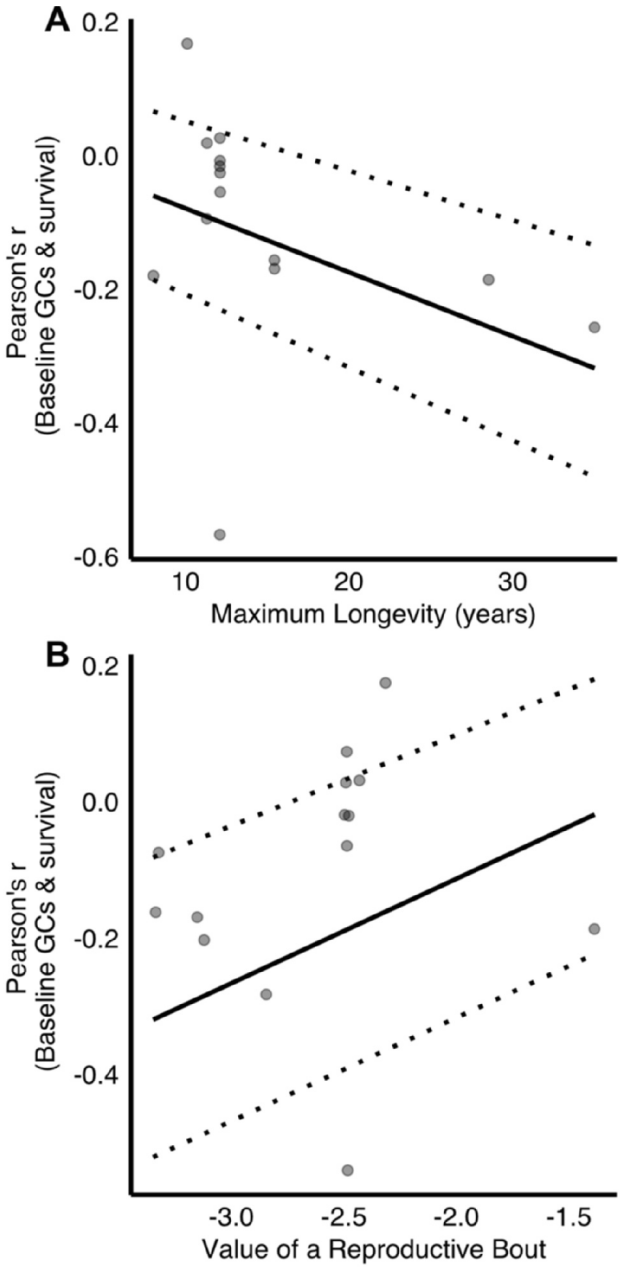

Fig. 2. The relationship between baseline GCs and survival varies according to (A) longevity and (B) the value of a reproductive bout (higher values indicate a relatively higher value of the current brood) (n = 14, species = 8). Each point represents an effect size and the dashed lines indicate 95% confidence intervals.

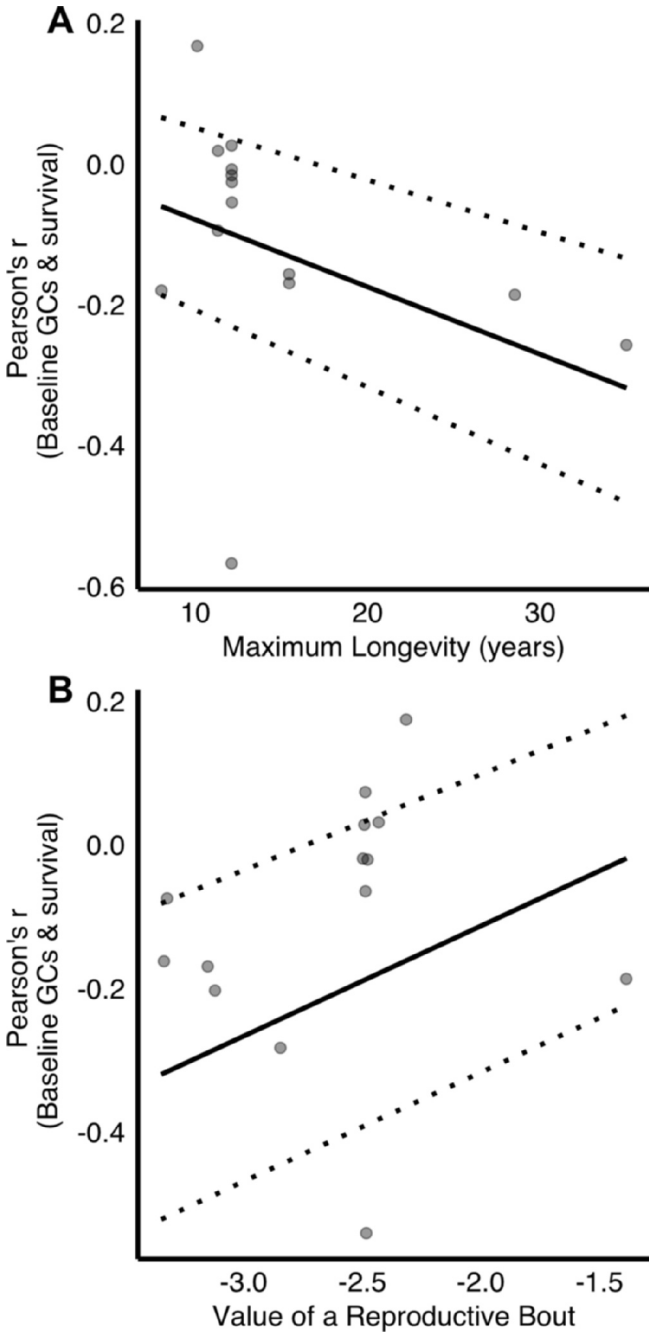

Fig. 3. The relationship between stress-induced GCs and survival varies according to (A) longevity and (B) the value of a reproductive bout (higher values indicate a relatively higher value of the current brood) (n = 11, species = 6). Each point represents an effect size and the dashed lines indicate 95% confidence intervals.

GCs and reproductive success (Fig. 1). Moderators did not explain any of the observed variation in effect sizes (sex (male): $\beta = -0.086$, 95% CI = −0.20 to 0.036, $p = 0.17$, n = 15; value of a reproductive bout: $\beta = -0.014$, 95% CI = −0.96 to 0.068, $p = 0.74$, n = 16; longevity: $\beta = 0.0062$, 95% CI = −0.0085 to 0.021, $p = 0.41$, n = 16).

3.6. Fecal GCs and fitness

Overall, fecal glucocorticoids were negatively associated with survival, but the relationship was not significant after incorporating the expected covariance in traits among related species (Fig. 1). Because there were no data for females, we were unable to test for an effect of sex. None of the other moderators (value of a reproductive bout: $\beta = 0.30$, 95% CI = −0.57 to 0.85, $p = 0.53$, n = 10; longevity: $\beta = -0.015$, 95% CI = −0.05 to 0.015, $p = 0.32$, n = 10) accounted for the remaining heterogeneity in the data.

No relationship was uncovered between fecal GCs and reproductive success with either the standard or phylogenetically informed meta-analyses (Fig. 1). Because there were no effect sizes for males, we were unable to test for an effect of sex. Although substantial heterogeneity exists in the data, none of the moderators explained this variation (value of a reproductive bout: $\beta = 0.037$, 95% CI = −0.44 to 0.49, $p = 0.89$, n = 12; longevity: $\beta = 0.13$, 95% CI = −0.26 to 0.48, $p = 0.51$, n = 12).

3.7. Experimentally elevated GCs and fitness

Both the standard and phylogenetically informed meta-analyses showed that experimentally increasing GCs reduced survival (Fig. 1). None of the life history moderators (sex (male): $\beta = -0.25$, 95% CI $= -0.52$ to 0.075, $p = 0.13$, n = 5; value of a reproductive bout: $\beta = 0.46$, 95% CI $= -0.15$ to 0.82, $p = 0.13$, n = 6; longevity: $\beta = -0.0098$, 95% CI $= -0.023$ to 0.003, $p = 0.13$, n = 6) explained the remaining heterogeneity in the data; however, this is unsurprising given the small sample size. The effect of GC manipulation on survival was associated with the length of time between administering treatment and assessing survival. More time before assessing survival yielded more negative relationships between GC treatment and survival, though the effect is very small ($\beta = -0.0005$, 95% CI $= -0.0009$ to 0.000, $p = 0.036$, n = 6).

Overall, experimental elevations of GCs reduced reproductive success, but this relationship was not significant after incorporating the expected covariance among related species (Fig. 1). None of the life history moderators (sex (M): $\beta = 0.016$, 95% CI $= -0.45$ to 0.47, $p = 0.95$, n = 12; value of a reproductive bout: $\beta = 0.46$, 95% CI $= -0.85$ to 0.98, $p = 0.58$, n = 15; longevity: $\beta = -0.016$, 95% CI $= -0.049$ to 0.017, $p = 0.34$, n = 15) or time from treatment until measuring reproductive success ($\beta = 0.0002$, 95% CI $= -0.0011$ to 0.0016, $p = 0.73$, n = 14) explained the heterogeneity in effect sizes.

3.8. Tests for publication bias

Egger's test for bias, the trim-and-fill test for missing data, and an investigation of patterns in effect sizes across time indicate no evidence for publication bias for the meta-analyses of baseline GCs and survival, stress-induced GCs and either survival or reproductive success, fecal GCs and either survival or reproductive success, and GC manipulation and reproductive success (details in Appendix A).

We observed evidence for time-lag bias in both the overall (Fig. 4) and bird-only meta-analyses baseline GCs and reproductive success: in both analyses, effect sizes increased with publication year, generally becoming closer to 0 in more recent years (overall baseline GC-reproductive success: $\beta = 0.03$, t = 4.28, $p < 0.0001$; birds-only: $\beta = 0.04$, t = 4.39, $p < 0.0001$). Neither Egger's test nor trim-and fill-analysis provided evidence for bias for the baseline GC-reproductive success analyses (see Appendix A).

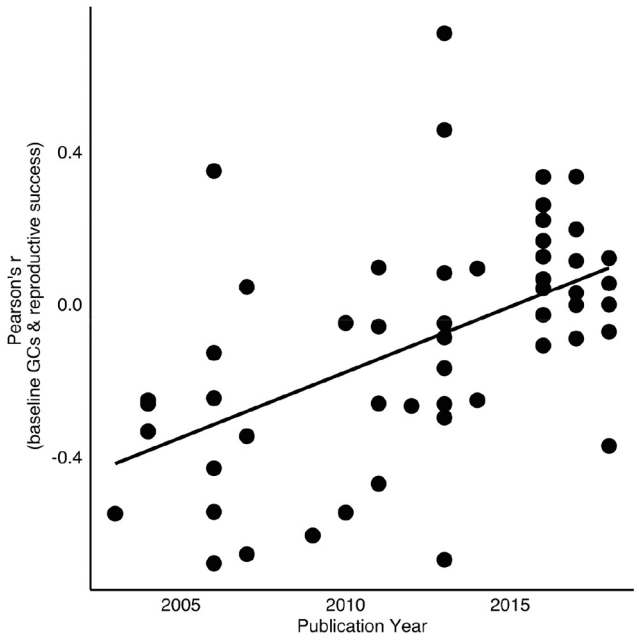

Fig. 4. Effect sizes of the relationships between baseline GCs and reproductive success increase over time, approaching 0. The more negative effect sizes observed in earlier publications could be the result of publication bias favoring more negative GC-fitness relationships.

The test for bias in the meta-analysis of the effects of experimental GC elevation on survival indicated that there is asymmetry in the funnel plot (Fig. S1, Appendix A), which can indicate publication bias. Although the Egger's test provided no evidence of bias for (z = 0.20, $p = 0.84$), the trim and fill analysis suggested that there is some evidence for publication bias and estimated that 1 effect size was missing. The trim-and-fill test allows for "filling" in the missing effect size and recalculating the parameters of the meta-analysis. Adjusting for the missing effect size did not change the overall direction of the relationship between experimentally elevated GCs and survival, but the effect was no longer significant (r $= -0.10$, 95% CI $= -0.26$ to 0.07, $p = 0.24$). Because both the effect size and sample size (n = 6) for this analysis were relatively small, they are particularly sensitive to adjusting for missing effect sizes. This result suggests that more data is necessary to draw strong conclusions about the effects of experimental GC elevation on survival. There was no relationship between publication year and effect sizes ($\beta = -0.013$, t $= -1.2$, $p = 0.29$). No other test of publication bias indicated a need to re-evaluate results, and the details of those analyses are described in the supplementary material.

4. Discussion

4.1. Plasma GCs and survival

As predicted, neither baseline nor stress-induced GC levels showed consistent directional relationships with survival. Baseline GC levels tended to negatively predict survival, but this relationship was not significant when incorporating the expected covariance between related species. Instead, our results support the prediction that life history strategy will influence the nature of the relationship between GC levels and survival. Among long-lived species, individuals with higher baseline GC levels had lower survival, a pattern that was not apparent in shorter-lived species (Fig. 2A). Longer-lived species may suffer greater phenotypic costs of elevated GC levels (including oxidative stress, accelerated telomere shortening, and tissue damage), because these costs can take longer to accumulate (Gassen et al., 2017; Metcalfe and Alonso-Alvarez, 2010; Sapolsky, 1999). We also predicted that because elevated baseline GC levels may help to support energetically demanding life history stages (Bonier et al., 2009a; Crespi et al., 2013; Moore and Jessop, 2003), higher baseline GC levels would be relatively more beneficial to reproductive success in species investing more in high value reproductive attempts (Bókony et al., 2009; Vitousek et al., 2019). Although the data reveal a trend in this direction, the relationship was not significant (Fig. 2B). Thus, baseline GC-survival relationships seem to be influenced more strongly by lifespan than by reproductive bout value.

The relationship between stress-induced GCs and survival also differed strongly by life history strategy. Mounting a stronger GC stress response was negatively associated with survival among longer-lived species, but the relationship was neutral or positive among shorter-lived species (Fig. 3A). This is consistent with the idea that responding effectively to stressors by mounting a strong GC response may be relatively more beneficial in organisms facing greater threats to survival (Angelier et al., 2009; Hau et al., 2010; Schoenle et al., 2018b; Vitousek et al., 2019), as well as the potential for the cumulative costs of elevated GC levels to be greater in longer-lived animals (Gassen et al., 2017; Lupien et al., 2009). Organisms with higher reproductive bout value also showed a more positive relationship between stress-induced GCs and survival than those with lower reproductive bout value (Fig. 3B). This relationship is not one that we predicted, but is consistent with the idea that GCs mediate trade-offs between investment in survival and reproduction (Breuner et al., 2008; Wingfield and Romero, 2001), with

a robust GC response conferring a survival benefit among species that invest heavily in a small number of reproductive attempts. While GCs can mediate this trade-off within some species, that same trade-off will not necessarily operate the same way across species (Agrawal, 2020). Taken together, these results suggest that the GC stress response may be particularly influenced by life history trade-offs in species with high reproductive bout value (with stronger GC responses favoring survival at a cost to reproduction). In contrast, both survival and reproductive success appear to favor lower GC responders in species that invest less heavily in individual reproductive attempts.

A limitation of this analysis, and of the analysis of plasma GCs and reproduction (see Section 4.2), lies in that the majority of studies measuring plasma GCs and fitness metrics are conducted in birds (Table 1). We accounted for phylogenetic relationships in our analyses, but additional effect sizes from reptiles, fish, and mammal would improve our ability to generalize these results across taxa. Future efforts in characterizing GC-fitness relationships would benefit from additional research in taxa other than birds.

4.2. Plasma GCs and reproductive success

Across studies, individuals with higher GC levels (both baseline and stress-induced) had lower reproductive success. These findings are consistent with the prediction that acute increases in GCs divert resources away from reproduction and towards immediate survival (Breuner et al., 2008; Wingfield and Sapolsky, 2003). Life history did not influence the relationship between stress-induced or baseline GCs and reproductive success. More surprising was the finding of a consistently negative relationship between baseline GC levels and reproductive success. Although elevated baseline GCs are often seen in individuals facing challenges, baseline GCs are also frequently upregulated before the onset of predictable, energetically demanding life history stages, and are believed to help organisms mobilize energy to meet these demands (Bonier et al., 2009a; Casagrande et al., 2018; Romero et al., 2000; Vitousek et al., 2019).

We found no consistent difference in the relationship between baseline GCs and reproductive success across the breeding stages of incubation and chick-rearing in birds. We expected this relationship to vary across breeding stages because the energetic demands of parents differ over the course of breeding (Martin, 1987; Westerterp and Bryant, 1984), and studies within avian species demonstrate that the relationships between GCs and reproductive success can change across breeding stages (Bonier et al., 2009b; Ouyang et al., 2011; Vitousek et al., 2018). Variation in the selective pressures facing different species or populations across breeding stages and environments could mean that GC-reproductive success relationships vary across breeding in some species, but not others. It is also possible that the time-lag bias caused by the publication of substantially more negative effect sizes in baseline GC-fitness relationships in the early 2000s (Fig. 4) skewed the results of this analysis, reducing our ability to detect context-dependence.

4.3. Fecal GC-fitness relationships

Observed patterns for fecal GCs and fitness can be explained by the expected similarity in trait values of related species; re-analyzing these patterns in a phylogenetic framework eliminated the statistical significance of these patterns. Fecal GCs reflect circulating hormone levels over longer time periods than baseline or peak stress-induced levels. Depending on the context of the organism, longer-term measurements of hormone levels obtained from feces or feathers may be more closely associated with either baseline (Bortolotti et al., 2008; Cavigelli et al., 2005; Good et al., 2003) or stress-induced GCs (Fairhurst et al., 2013; Harper and Austad, 2002). Although the relationships between GCs and survival are complex and context-dependent, we saw a consistently negative relationship between reproductive success and both baseline and stress-induced GCs. Why then do we not see this relationship in fecal GCs? One possibility is that the presence of these relationships is obscured by inter-individual variation in diet, metabolic rate, or hormone metabolite formation (Goymann, 2012). Measured fecal GC concentrations can also be affected by variation in the time between defecation and collection/freezing, and by environmental factors such as temperature, precipitation, and microbial content (Dantzer et al., 2014). In addition, mammals were not represented in the datasets of baseline and stress-induced GCs (primarily birds), but comprised the majority of the effect sizes in the fecal GCs dataset (Table 1). Thus, GC-reproductive success relationships might differ among the main taxa represented in these analyses – mammals and birds.

4.4. Experimentally elevated GCs and fitness

Experimentally elevated GC levels were consistently negatively associated with survival. Tests for publication bias revealed that some bias is present such that one effect size appears missing. When adjusting for this missing effect size, the relationship between experimental GCs and survival remained negative, but was no longer statistically significant. Individuals with manipulated GC levels tended to have lower reproductive success – a pattern that mirrors the relationships seen in unmanipulated individuals – but this effect was not significant in analyses that incorporated phylogenetic relationships. These results align with those of a recent meta-analysis which found GC manipulations reduced fitness when assessed as either survival or reproductive success (Bonier and Cox, 2020).

Although experimentally altering GC levels generally reduced survival, this pattern is interesting considering that natural variation in GCs showed variable and context-dependent relationships with survival. This discrepancy could result from several factors. Hormone manipulations often do not accurately mimic natural variation in circulating GCs across various temporal scales (Fusani, 2008). Additionally, because hormone regulation can be adaptively modulated in accordance with the internal and external context of an individual, it is not surprising that manipulations that move individuals away from their natural regulatory patterns could negatively impact fitness, even if similar relationships are not seen in unmanipulated individuals (Bonier and Cox, 2020; Crossin et al., 2016; Schoenle et al., 2019). Intriguingly, experimentally altered GC levels were associated with a greater decrease in survival in studies that measured survival over longer time periods. This is consistent with the potential for many of the salient costs of GCs to accumulate over longer timescales. Although most studies assess only the short-term survival impacts of GCs, these patterns suggest that GC manipulations could be more costly than previously assumed.

5. Conclusions

Our results suggest that life history context is crucial to understanding the relationships between GCs and survival. Although plasma GCs were not consistently associated with survival, the direction of both baseline and stress-induced GC-survival relationships were strongly dependent on life history. In contrast, our meta-analysis demonstrates consistently negative relationships between plasma GCs and reproductive success, but life history context was not associated with the variation in the direction of the relationship. Unlike measurements of plasma GCs, fecal GCs did not show consistent relationships with either survival or reproductive success. Our analyses support the potential for GC elevation to have pathological effects: experimental GC elevation reduced survival, whereas its effect on reproductive success was less clear. We recommend that moving forward, researchers aim to explicitly test how the optimal GC response to challenges varies across contexts, including those not measured in these meta-analyses. Studies manipulating challenges (including the frequency and intensity of these challenges) and GCs across environmental gradients as well as life history stages and strategies could provide insight into how different

contexts may influence GC–fitness relationships. Finally, our search of the literature revealed gaps in our knowledge of GC-fitness relationships. Nearly all observational studies were conducted during the breeding season, and more than twice as many of the available effect sizes were from tests of the GC-reproductive success relationship than of the GC-survival relationship (Table 1). Furthermore, the available GC-fitness effect sizes are highly biased towards birds, even though it seems like relevant data should exist for other taxa given the interest in stress physiology across all vertebrates (reviewed for primates in Beehner and Bergman, 2017; Romero and Wingfield, 2016). To develop a more comprehensive understanding of the relationships between GCs and fitness, we also encourage future studies to extend beyond the breeding season and to incorporate survival analyses in more diverse taxa.

CRediT authorship contribution statement

Laura A. Schoenle: Conceptualization, Investigation, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Cedric Zimmer:** Investigation, Methodology, Writing - review & editing. **Eliot T. Miller:** Methodology, Formal analysis, Writing - review & editing. **Maren N. Vitousek:** Conceptualization, Investigation, Methodology, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygcen.2020.113611.

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