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RESEARCH ARTICLE

Maternal Testosterone and Offspring Sex-Ratio in Birds and Mammals: A Meta-Analysis

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Abstract Sex allocation theory predicts that parents should bias offspring sex to maximize their fitness in a given context. Quantifying the fitness benefits of offspring sex-ratio biases would be facilitated by a better knowledge of their underlying mechanism(s) and associated costs. The hypothesis that steroid hormones are involved in sex determination has gained in popularity recently. Being influenced by external stimuli and involved in a range of physiological processes, they could be a ubiquitous mediator of environmental conditions influencing sex-ratio with low fitness costs. Previous studies indicated that higher maternal testosterone levels led to the overproduction of sons around conception in both birds and mammals. We conducted a systematic review (including meta-analysis) of these studies and, as predicted, we found a weak positive and significant overall effect of maternal testosterone on the proportion of sons. Neither taxa, nor the type of study (experimental/observational), or the timing of timing testosterone manipulation/measure were significant predictors of offspring sex-ratio, which may be explained by low statistical power in addition to low variability between effect sizes. Our meta-analysis provides evidence for a general positive influence of maternal testosterone around conception on the proportion of sons across birds and mammals, although less confidently so for the latter. It begs for more large-scale experimental studies, especially on mammals, and ideally in the wild. It may also have some important consequences for the poultry industry.

Keywords Differential mortality · Poultry · Sex ratio · Proximate mechanism · Sex determination · Steroids

Introduction

Offspring sex-ratio is a key component of reproductive allocation and parents may be selected to adjust it according to environmental conditions. Evidence for adaptive sex-ratio biases have been found in a wide range of taxa, but they have been more convincing in those with strong control over sex determination and/or high fitness benefits of sex-ratio adjustment, such as haplo–diploid parasitic wasps (West 2009). However, patterns remain inconsistent and somewhat inconclusive in birds and mammals, in part due to the difficulty of determining the fitness benefits of sex-ratio adjustment in taxa with more complex life-histories (Cockburn et al. 2002; Komdeur 2012; Komdeur and Pen 2002). Another important piece of information still missing is the nature of the underlying mechanism(s) of offspring sex-ratio adjustment. A number of hypotheses have been proposed (Alonso-Alvarez 2006; Krackow 1995), and there are some convincing case studies (Cameron 2004; Grant et al. 2008; Komdeur et al. 2002), but it remains unclear whether a single mechanism has been selected across species or whether different mechanisms coexist.

Any adaptive mechanism should enable the internal translation of external stimuli into a deviation from the expected 50:50 sex-ratio as soon as possible after meiosis. The social and environmental factors (e.g., food availability, number of helpers) potentially influencing offspring fitness in a sex-specific way should be translated into a physiological signal

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that in turns influences sex-ratio. Across vertebrates, the role of the endocrine system is precisely to regulate physiological activities in response to changes in the environment. Hence, it is logical that hormones, steroid hormones in particular, have been suggested as ideal candidates for linking external conditions to variation in offspring sex-ratio across taxa (Grant and Chamley 2010; Navara 2013a). Steroid hormones are strongly influenced by external stimuli such as temperature and social context and are involved in a wide range of physiological processes, including the operation of the sexual system and even the cytological processes at the time of meiosis (Rutkowska and Badyaev 2008; Uller and Badyaev 2009). It is therefore not surprising to find evidence of steroid-mediated sex-ratio adjustment in taxa such as fish, reptiles, birds and mammals (Navara 2013a).

The most commonly studied steroid, testosterone, has been implicated in some of the most convincing sex-ratio biases observed, including in birds and mammals, with higher levels of maternal testosterone often leading to the overproduction of sons (Navara 2013a). Those similar effects in avian and mammalian species, in conjunction with the conserved endocrine functions and the comparable selective pressures on sex allocation (Cockburn et al. 2002), raise the possibility that natural selection favoured a generalised pathway between external conditions and offspring sex-ratio bias via variation in maternal testosterone. This is corroborated by the fact that variation in environmental conditions such as social context (e.g., mate quality, breeding density) leads to, sometimes rapid, changes in maternal testosterone in both taxa (e.g., Gleason et al. 2009; Mazuc et al. 2003). However, because the heterogametic sex differs between the two taxa, it is likely that the cytological mechanism leading to sex-ratio bias is not identical (Navara 2013a). In mammals, where females are the homogametic sex (XX), higher testosterone concentrations in the follicular fluid may influence the composition of the extracellular matrix (zona pellucida) to render an emerging ovum to be more likely to receive a Y-chromosome-bearing spermatozoon (Grant and Chamley 2010). In birds, where females are the heterogametic sex (ZW), testosterone may bind directly to the oocyte (or act through other mediators) when the first meiosis occurs and lead to segregation distortion, with higher levels of testosterone leading to a Z-chromosome bearing ovum (Pinson et al. 2011b; reviewed in; Rutkowska and Badyaev 2008; Uller and Badyaev 2009), although other targets for the action of testosterone pre-fertilisation have been suggested (Navara 2013b). Importantly, both mechanisms would involve low costs of sex allocation in terms of parental investment (energy and time) as compared to other post-fertilisation mechanisms such as selective embryo mortality (see Krackow 1995; Robert and Schwanz 2011). Maternal testosterone thus has the potential to be a mechanism selected for across birds and mammals. Although testosterone has been shown to influence sex determination in other taxa, such as reptiles (Lovern and Wade 2003) or fishes (Pandian and Sheela 1995), the evolutionary pathway might not be comparable to birds and mammals as sex determination mechanisms are more complex and diverse in those taxa (e.g., environmental vs. genotypic sex determination, sex reversal). Hence, we chose to test the hypothesis that maternal testosterone could be part of a general mechanism underlying sex-ratio biases in birds and mammals. We tested this hypothesis by conducting a systematic review (including a meta-analysis) of studies investigating the relationship between maternal testosterone and offspring sex-ratio. The aim of such an approach is to find all the studies on a specific topic and to quantify the strength of the overall effect, as well as to identify the potential sources of variation among studies. We thus first determined the overall effect of maternal testosterone on offspring sex-ratio (proportion of sons) and its magnitude. We then quantified heterogeneity among studies (i.e. how variable the effect sizes are) and, finally, tested hypotheses regarding the potential causes of heterogeneity across studies (experimental vs. observational studies; bird vs. mammal; time to conception: see Table 1 for specific predictions).

Table 1 List of moderators included in the meta-regression investigating the relationship between maternal testosterone and offspring sex-ratio

Moderator	Prediction
Study type (experimental or observational)	The effect size will be greater among experimental than among observational studies, because of the higher control of external parameters in experimental studies
Taxa (bird or mammal)	The effect size will be greater among birds than among mammals, because females are the heterogametic sex in birds
Timing of testosterone measure/manipulation	The effect size will decrease the further away from conception testosterone has been measured/manipulated, because testosterone is predicted to act at conception
Timing of sex-ratio measure (primary or secondary)	No a priori prediction
Origin of animals (captive or wild)	No a priori prediction
Publication year	No a priori prediction

Materials and Methods

Literature Search and Inclusion Criteria

We performed a systematic literature search and presented it as the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart (Moher et al. 2009) (Figure S1). In line with the recent push for more transparent and credible research (Ihle et al. 2017; Parker et al. 2016), our literature search and subsequent analyses were preregistered on the Open Science Framework website to avoid post-hoc interpretation of our results (https://osf.io/vfnhg/register/565fb3678c5e4a66b5582f67). The initial search was performed on October 11th 2016, on titles, abstracts and key words, in both the Web of Science and Scopus databases. We used the following keyword combinations: '(testosterone OR androgen*) AND (bird* OR avian OR mammal* OR livestock OR "farm* animal*" OR poultry OR mice OR rat OR rats OR rattus OR "guinea pig*" OR chick* OR turkey* OR sheep OR pig* OR cow*) AND ("sex ratio*" OR "sex-ratio*" OR "offspring sex" OR "sex of the offspring" OR "sex allocat*" OR "embryo sex" OR "fetal sex" OR "foetal sex" OR offspring OR nestling* OR clutch OR brood* OR litter* OR birth*) AND NOT (lizard OR fish OR turtle* OR chelonia* OR crocodil* OR yolk OR "in vitro" OR cell* OR neuro* OR disrupt* OR disease OR infect* OR castrat* OR psychol* OR *nutri* OR toxi* OR obes* OR diabet* OR cancer* OR ethanol)'.

The online database search yielded 1370 potentially eligible articles (Figure S1). Two authors independently duplicate-screened 350 article abstracts with an 80% agreement rate, using AbstrackR software (Wallace et al. 2012). The screening of the remaining abstracts was shared between the same two persons and in unclear cases both persons screened the abstract. Other sources of potentially relevant studies comprised reference lists (backwards search) and lists of citing publications (forward search) of included papers and appropriate reviews (Grant 2007; Grant and Chamley 2010; Navara 2013a, b), as well as results from searches on other databases (Trove, Google Scholar and Google). Overall, we screened titles and abstracts (if promising title) of ~1000 papers from these additional sources (Figure S1). From the resulting ~2000 unique studies we identified 194 studies fulfilling the title and abstract criteria (see supporting information) and suitable for full-text examination (Figure S1). Inclusion criteria applied to the 194 full-texts were: (i) maternal testosterone (not yolk testosterone) was measured or manipulated before or shortly after the eggs were laid/offspring were conceived, (ii) offspring sex-ratio of mothers with known testosterone levels/subject to the testosterone manipulation was measured and (iii) suitable information about statistics and sample sizes ($N >= 5$) were reported in the paper or there was indication that the needed information could be provided by the authors. After applying these criteria, 16 studies (for a total of 23 effect sizes) with suitable data remained (Table 2). Details and reasons for exclusion of the other studies are given in Table S1.

Yolk hormones have also been suggested to influence sex determination (Navara 2013b) and a few studies have tested this hypothesis. To provide a more complete view of the influence of testosterone on sex determination, we included an exploratory meta-analysis investigating the correlation between yolk testosterone and offspring sex that was not part of the initial preregistration (see supporting information for more details and results).

Effect Size Extraction/Calculation

For observational studies, we calculated Spearman's correlation coefficients between maternal testosterone and offspring sex-ratio, and converted them to Fisher's *Z* (hereafter termed '*Zr*'). For experimental studies, means, standard errors and sample sizes were extracted, and used to calculate Hedges' unbiased standardized mean differences (Hedges' *d*: Hedges and Olkin 2014), before converting them to *Zr* to allow comparison with observational studies. When data were provided in a figure, we extracted values using WebPlotDigitizer 3.8 (http://arohatgi.info/WebPlotDigitizer/).

For each study included, we recorded study and species identity to account for potential correlated structures within the data. We also collected information on the following moderator variables to explain heterogeneity in the data: taxon (bird or mammal), type of study (experimental vs. observational), timing of testosterone manipulation or measurement (number of days between implant/injection and conception or mean number of days between testosterone sampling and conception), publication year, origin of animals (captive vs. wild), timing of offspring sex-ratio measurement (primary vs. secondary), species reproductive mode (monotocous vs. polytocous), tissue of testosterone measure/manipulation, mode of testosterone administration (if manipulated) and type of testosterone measurement assay. However, we did not consider the final four moderators in statistical analyses, because our effect size number was relatively small and we did not have strong a priori predictions regarding their potential effects. Distribution of the effect sizes according to the main categorical moderators is given in Table S2.

Meta-Analyses and Publication Bias

We created a phylogenetic tree containing all the species using the Interactive Tree of Life online tree generator (http://itol.embl.de/) via the *rotl* package (Michonneau et al. 2016, Figure S2). The phylogenetic tree obtained from the Interactive Tree of Life online tree generator contained only

Table 2 Summary of the studies included in the meta-analysis

Taxa	Species	Number of effect sizes extracted[a]	Timing of manipulation/ measure	Primary or secondary sex-ratio	Sample size[b]	Reference
Mammal	Rat	0/1	−5	Secondary	13	Arnon et al. 2016
Bird	Japanese quail	0/1	0	Primary	25	Correa et al. 2011
Mammal	Assamese macaque	0/1	7	Secondary	6	Fuertbauer et al. 2012
Bird	Homing pigeon	2/2	−11; −12/2; 3	Primary	C:20–T:23; C:20–T:21/44; 38	Goerlich et al. 2009
Bird	Homing pigeon	0/1	−1	Primary	24	Goerlich et al. 2010
Mammal	Barbary macaque	0/1	−45	Secondary	9	Grant et al. 2011
Mammal	Field vole	0/1	−14	Secondary	28	Helle et al. 2008
Mammal	Cow	1/0	−50	Secondary	C:11–T:4	Kesler et al. 1995
Mammal	Red deer	0/1	12	Secondary	16	Pavitt et al. 2016
Bird	Peafowl	0/1	10	Primary	18	Pike and Petrie 2005
Bird	Japanese quail	1/1	−2/10	Primary	C:8–T:8/45	Pike and Petrie 2006
Bird	Chicken	1/0	−0.2	Primary	C: 69–T: 25	Pinson et al. 2011b
Bird	Zebra finch	4/0	−2; −3; −4; −5	Primary	C:16–T:15; C:16–T:16; C:15–T:16; C: 9–T:8	Rutkowska and Cichoń 2006
Mammal	Mandrill	0/1	−35	Secondary	12	Setchell et al. 2015
Mammal	Nubian ibex	0/1	−75	Secondary	7	Shargal et al. 2008
Bird	Spotless starling	1/0	−60	Secondary	C:20–T: 16	Veiga et al. 2004

[a]From experimental data/from observational data

[b]Number of mothers considered in a study. From experimental data/From observational data. For experimental data, separated into number of control mothers (C) and experimental mothers (T)

taxa topology without branch lengths. Accordingly, we converted this topological tree to an ultrametric tree with simulated branch lengths (using the *compute.brlen* function from the *ape* package, see Figure S2), so that the phylogenetic correlation could be incorporated in our meta-analyses. We then checked whether random effects needed to be included. Multiple effect sizes from the same species, same study, or from species with phylogenetic relatedness could lead to biased estimates, if not properly controlled for. We used multilevel meta-analyses (Viechtbauer 2010) where each variable (study ID, species ID and phylogenetic relationships) was included as a random factor in an intercept-only model and compared to a model without random effects using a likelihood ratio test (using maximum likelihood 'ML' estimates). Because all *p*-values were exactly 1, and the estimates and standard errors of the models with random effects were identical to those without, we ran the main statistical analyses presented in the paper without random effects.

Intercept-only models using restricted maximum likelihood estimation provided the overall effect size and the heterogeneity statistic I^2, which represents the percentage of variability in the effect sizes that is not due to sampling error (Higgins et al. 2003). Moderator analyses were conducted using meta-regression models where continuous variables were standardized (to mean of 0 and SD of 1). In meta-regression models, due to the small number of effect sizes ($k = 23$), we considered only moderators for which we had a priori predictions (Table 1). In addition, and although not originally pre-registered, we also tested for the effects of the timing of sex-ratio measure (primary or secondary) and the origin of animals (captive/wild). We conducted AICc model selection (Burnham and Anderson 2002) on models containing zero to two of the moderators, using ML estimation in the *MuMIn* package (Bartoń 2016). We ran Egger's regression test (Egger et al. 1997) and a trim-and-fill analysis (Duval and Tweedie 2000) to test for publication bias. Also, we tested for a time-lag bias (Jennions and Møller 2002) using publication year as a moderator. All analyses were conducted using the *metafor* package (Viechtbauer 2010) in R 3.3.1 (R Core Team 2015).

Results

Overall, there was a weak positive and significant effect of maternal testosterone on proportion of sons ($Zr_{overall} = 0.142$; 95% CI [0.060, 0.224]) and heterogeneity in the data was very low ($I^2 = 16.5\%$: *sensu* Higgins et al. 2003). None of the moderators explained a significant amount of variance among effect sizes (Fig. 1; Table 3). The meta-analytic model (i.e. without moderators) was the best model of all the models tested, and the nearest one was the

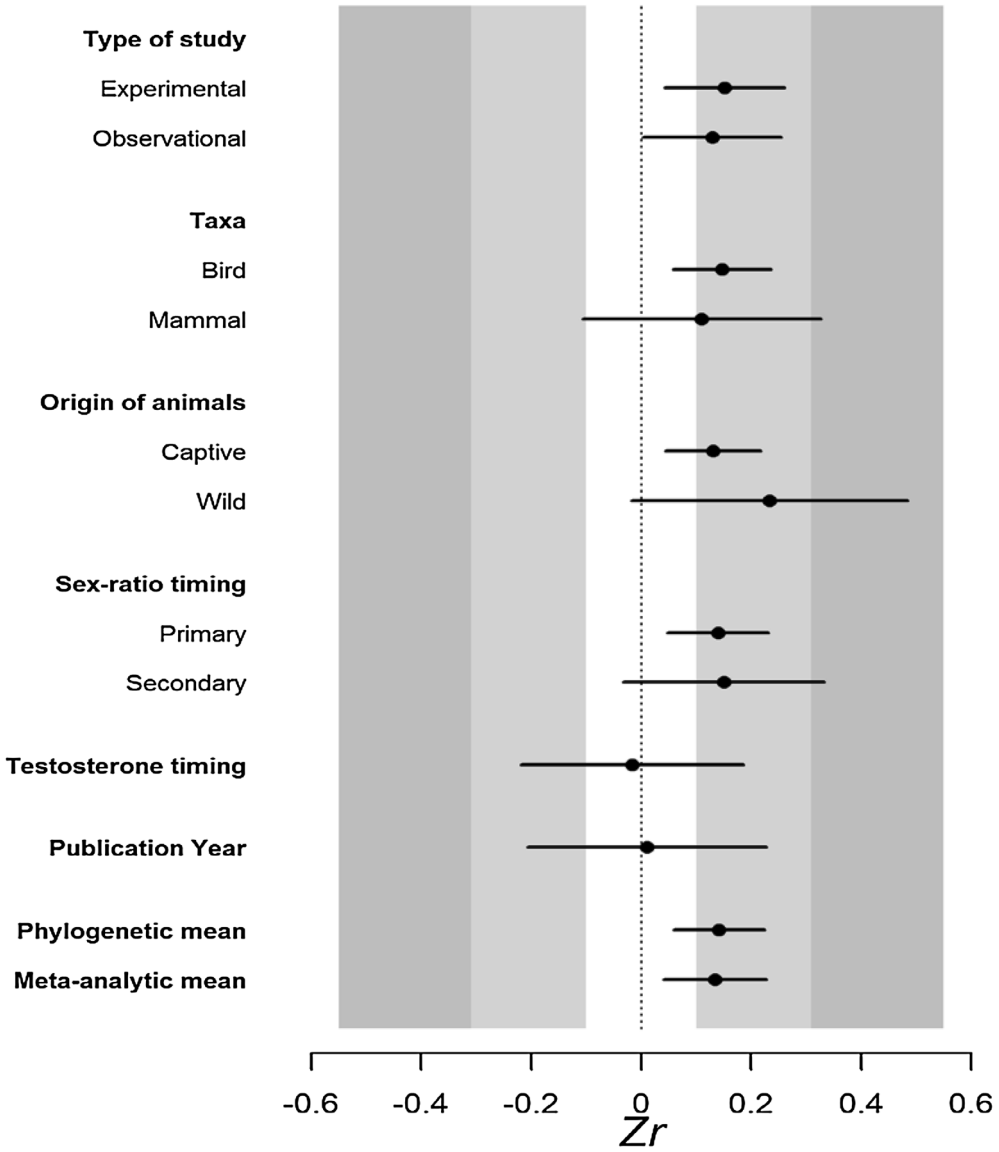

Fig. 1 Meta-analytical and meta-regression parameter estimates for studies investigating the effect of maternal testosterone on the proportion of sons. Circles represent mean estimates and error bars show 95% confidence intervals. White, light-grey, and grey regions represent regions for small (0–0.1), small-to-medium (0.1–0.3) and medium-to-large (0.3–0.55) effect sizes, respectively. Phylogenetic mean stands for meta-analytic mean with phylogenetic relatedness controlled for

model with testosterone timing (Table 3). We ran sensitivity analyses to check for the robustness of the results, and found that that the overall effect always remained weak but significant (see supporting information). Publication bias was weak or absent: the funnel plot did not deviate from symmetry (Figure S3), as confirmed by the non-significant Egger's regression test ($z = -0.330$; $P = 0.74$). The trim-and-fill analysis did not reveal any publication bias either (see supporting information). There was little evidence of time-lag bias, as the model with publication year was 2.35 ΔAICc behind the model without any moderators (i.e. the null model).

Discussion

We systematically reviewed the evidence concerning the influence of maternal testosterone near conception on offspring sex ratio, and found a weak positive and significant effect on the proportion of sons produced (Fig. 1). Our results therefore support the role of maternal testosterone as a ubiquitous mediator of environmental conditions influencing sex determination across birds and mammals. However, caution is required in the interpretation of these results given the small number of studies available and their relatively small sample sizes. We will therefore

Table 3 AICc model selection table from the moderator analysis showing models within 4 ΔAICc of the best model (none of the models with two moderators were good enough to be in this subset)

Model	*k*	logLik	AICc	ΔAICc	ωAICc
Null	1	−1.783	5.757	0	0.278
Testosterone timing	2	−1.342	7.283	1.527	0.129
Captive/wild	2	−1.496	7.592	1.835	0.111
Taxa	2	−1.735	8.070	2.313	0.087
Experimental/observational	2	−1.748	8.097	2.340	0.086
Publication year	2	−1.757	8.113	2.357	0.085
Primary/secondary sex-ratio	2	−1.778	8.155	2.399	0.084
Primary/secondary sex-ratio + testosterone timing	3	−0.934	9.131	3.375	0.051
Testosterone timing + publication year	3	−1.097	9.457	3.701	0.044
Testosterone timing + taxa	3	−1.099	9.461	3.705	0.043

k is the number of parameters in the model; logLik is the model log-likelihood; AICc is the AIC score corrected for small sample size; ΔAICc is the difference between the best model and a given model and ωAICc is the model probability of being the best model

discuss what is needed to get to a more solid conclusion in the future.

There was no significant effect of taxon (bird vs. mammal), counter to the prediction that female heterogamety in birds allows greater control of offspring sex via meiotic or ovulatory mechanisms compared to female mammals that can only ovulate X eggs (Komdeur 2012). Yet, the confidence interval was narrower and did not overlap with zero for bird studies while it was wider and overlapped with zero for mammal studies, thereby suggesting that results should still be interpreted more cautiously for mammals. In all mammal studies, offspring sex-ratio was measured at birth (secondary sex-ratio), whereas all but one bird studies considered the primary sex-ratio. Although the effect size was similar between studies measuring primary or secondary sex-ratio, the confidence interval was larger for the latter ones. Altogether, the evidence for an influence of maternal testosterone on sex-ratio at conception is stronger in birds, although most studies still have a relatively small sample size. This influence is less clear-cut among mammals, most likely because of the combination of generally lower within-study sample sizes and low number of mammal studies. Also, because the primary sex-ratio was never measured in mammal studies, we cannot exclude that the observed sex-ratio biases are not due to differential mortality during gestation. Finally, another explanation for the weaker effect in mammals could be the paternal influence on offspring sex-ratio via X or Y-biased ejaculates. There is growing evidence that there is inter-individual variation in sperm X/Y ratio (Edwards et al. 2016; Edwards and Cameron 2014), with a recent study finding that this variation explained 22% of the variance in sex-ratio of the white-footed mouse (*Peromyscus leucopus*) (Malo et al. 2017). Hence, future studies on mammals should also investigate the mechanism(s) behind the variation in sperm X/Y ratio and how external conditions mediate it.

Contrary to what we predicted, observational studies had similar effect sizes to experimental ones and the timing of testosterone measure/manipulation relative to conception was not important. Although these findings could be biologically true, the relatively small effect size number, combined with the very low heterogeneity (i.e. variance among effect sizes), as compared to other meta-analyses in ecology and evolution (mean heterogeneity 91.69%, Senior et al. 2016) could also explain the absence of significant moderators and therefore lead us to interpreting our results carefully. Concerning the absence of effect of the timing of testosterone measure/manipulation, another potential explanation is the lack of consistency between protocols. Samples from different sampling tissues (e.g., plasma, faeces, hair) reflect testosterone concentrations over different time windows and different experimental manipulations (e.g., injection or implant) influence testosterone over different time windows. Testosterone measured or manipulated at a specific time before conception, thus, does not necessarily have the same meaning in different studies. Hence, we should ideally have controlled for confounding factors such as sampling tissue, experimental protocol or dosage, but the small number of studies prevented us from doing so. Cameron (2004) showed that the closest to conception maternal condition was measured, the stronger the effect on offspring sex-ratio was. We thus expect testosterone levels at conception to better explain sex-ratio, and future studies should aim to measure/manipulate testosterone at this time point (see Pinson et al. 2011b). Another fruitful avenue of research would be to measure how the change in testosterone explains sex-ratio variation, because a few studies have shown that changes in the response variable had a stronger effect than absolute values (e.g., Cameron et al. 2008; Cameron and Linklater 2007).

Our systematic review and meta-analysis confirms the important role of maternal testosterone in sex-ratio across birds and mammals and its relationship with the production

of sons. However, our study also highlights three major gaps in the existing evidence that should be the focus of upcoming studies. (1) Mammal studies had generally lower sample sizes than bird studies, they were almost all observational studies and only considered the sex-ratio at birth. Hence, a large-scale experimental study where sex-ratio is measured before birth, if possible, would greatly help. (2) So far, there has been only one experimental study in the wild (Veiga et al. 2004). Thus, there is a need for more studies of this kind. (3) Although our results confirm that testosterone may act at the time of meiotic segregation in birds (Pinson et al. 2011b), experiments manipulating testosterone at different timing relative to conception (for example days before conception vs. just before conception) would help to understand more precisely at which stage (or stages) testosterone is acting to influence offspring sex. Moreover, whereas the largest sample size so far has been less than 100 broods/litters, a power analysis revealed that to find a correlation of 0.15 with 80% power and a significance level of 0.01 or 0.05 would require having 520 and 350 broods/litters, respectively. This might unfortunately only be possible using captive animals such as chickens, quails, rabbits, mice, or rats.

Finally, although our study highlights the role of maternal testosterone as a mediator between environmental conditions and the outcome of sex determination, other mechanisms may occur concomitantly. For instance, stress hormones are also implicated in sex-ratio biases in both birds and mammals and higher levels of corticosterone are generally associated with the overproduction of daughters (Pinson et al. 2015, 2011a; reviewed in Navara 2013a; but see; Gam et al. 2011). Stress hormones may thus act antagonistically with testosterone (Navara 2010). Some studies have measured both hormones in relation to offspring sex-ratio (e.g., Arnon et al. 2016; Correa et al. 2011; Helle et al. 2008), but only one has found a positive effect of testosterone in conjunction with a negative effect of stress hormones (Pike and Petrie 2005). It has been suggested that downstream effects of stress hormones could influence testosterone levels, which in turn would be responsible for sex-ratio biases (Navara 2010). Hence, the picture is probably more complex and there is a need for studies experimentally manipulating both types of hormones to better understand their relative role in offspring sex-ratio adjustment.

Our meta-analysis contributes significantly to the field of sex allocation by providing quantitative evidence for a general positive role of maternal testosterone around conception on the proportion of sons across birds and mammals, although less confidently so for the latter. Such a general mechanism would confirm that most species have the ability to adaptively adjust sex-ratio. Hence, the lack of observation of sex-ratio adjustment would then be explained by the weakness of the selective pressures and not by physiological constraints (West and Sheldon 2002). As a follow-up from our study, we hope to encourage large-scale experimental studies especially on mammals, and ideally in the wild, to enhance the biological relevance of the results. Besides their fundamental importance, our conclusions may also have some applied implications, particularly for the poultry industry. Using anti-androgens to overproduce daughters could prevent the current sacrifice of most male chicks (because they cannot lay eggs), which would have considerable ethical and economic benefits.

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Data Accessibility All data and code are available on the Open Science Framework (https://osf.io/67q8d/).

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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