TECHNICAL COMMENT

The jury is still out regarding the generality of adaptive 'transgenerational' effects

Alfredo Sánchez-Tójar,[1]* iD
Malgorzata Lagisz,[2] iD
Nicholas P. Moran,[1] iD
Shinichi Nakagawa,[2] iD
Daniel W. A. Noble[3] iD **and**
Klaus Reinhold[1] iD

Abstract

A recent meta-analysis concluded, '*transgenerational effects are widespread, strong and persistent*'. We identify biases in the literature search, data and analyses, questioning that conclusion. Re-analyses indicate few studies actually tested transgenerational effects – making it challenging to disentangle condition-transfer from anticipatory parental effects, and providing little insight into the underlying mechanisms.

COMMENTARY

Anticipatory parental effects are a type of adaptive intergenerational plasticity where parents anticipate their offspring's (F1) environment, and *program* their phenotype accordingly (Marshall & Uller, 2007; Uller, 2008; Shea *et al.*, 2011). Importantly, for these effects to be considered truly transgenerational, they should be detectable at least in the F2 (grand-offspring) or F3 (great grand-offspring) generation, depending on the mode of reproduction, time of exposure, etc. (O'Dea *et al.*, 2016; Perez & Lehner, 2019). Despite several textbook-like examples of anticipatory parental effects (Tollrian, 1995; Fox *et al.*, 1997; Agrawal *et al.*, 1999; Galloway & Etterson, 2007), recent syntheses have challenged their generality (Uller *et al.*, 2013; Radersma *et al.*, 2018). Condition-transfer parental effects, where the physical condition of parents is positively related to their offspring's fitness (irrespective of offspring environmental quality), have been argued to contribute to the ambiguity found in previous syntheses (Bonduriansky & Crean, 2018; Engqvist & Reinhold, 2016, 2018). Yin *et al.* (2019) attempted to resolve the ambiguity found in previous syntheses by integrating results from experiments performed across species and environmental gradients. While we applaud the authors for their effort, we suggest there are limitations regarding how the study was conducted, reported and interpreted that challenge the reliability and generality of its conclusions.

The literature search had limited coverage, lacked transparency and was not reproducible. Coverage was reduced because of the following reasons: (1) Records were filtered by only two subject areas, 'environmental sciences ecology' and 'evolutionary biology', thus, excluding key areas such as 'zoology', 'reproductive biology' and 'developmental biology',

consequently excluding around 78% of potentially relevant records (Supporting Information 1.1). (2) Important keywords and their alternative spellings (e.g. 'trans-generational', 'inter-generational', 'silver-spoon', 'programming') were not included in the search string (Supporting Information 1.2). (3) The search strategy was inconsistent, for example, despite indicating that records containing the keyword 'diet(s)' were excluded (using NOT ('diet$') in the search string), 19 studies manipulating diet were included in the meta-analysis (Supporting Information 2.6). (iv) Non-fully factorial experiments published before January 2013 were also excluded, but they were included after 2013, which may have biased the results since non-fully factorial experiments produce larger effect sizes than fully factorial experiments (Supporting Information 2.9, 5.8).

The analyses did not fully account for non-independence among effect sizes. First, residual variance (i.e. unit-level effect), which needs to be modelled explicitly in meta-analyses, was not. Second, a nested data structure was assumed for the random effects, despite the data structure corresponding to a (partial) crossed design. Third, shared control (Lajeunesse, 2011) and phylogenetic non-independence (Chamberlain *et al.*, 2012) were not accounted for, despite the statements in Yin *et al.* (2019). Supporting Information 5 contains an overview of the sources of non-independence and a full re-analysis accounting for them.

Our re-analysis, which accounted for non-independence among effect sizes (see above), shows that effects are overall much more uncertain (wider 95% confidence intervals, CI) than shown in Yin *et al.* (2019), particularly when phylogenetic non-independence is accounted for. Indeed, the phylogenetically corrected overall effect of the ancestors' conditions is 0.10 (95% CI = [0–0.20]; Fig. 1; mean = 0.11 [0.06–0.16] when

[1]*Department of Evolutionary Biology, Bielefeld University, Bielefeld, Germany*
[2]*Evolution & Ecology Research Centre and School of Biological, Earth and Environmental Sciences, University of New South Wales, Sydney, Australia*
[3]*Division of Ecology and Evolution, Research School of Biology, The Australian National University, Canberra, Australia*

Correspondence: E-mail: alfredo.tojar@gmail.com
[The copyright line for this article was changed on 14 October 2020 after original online publication]
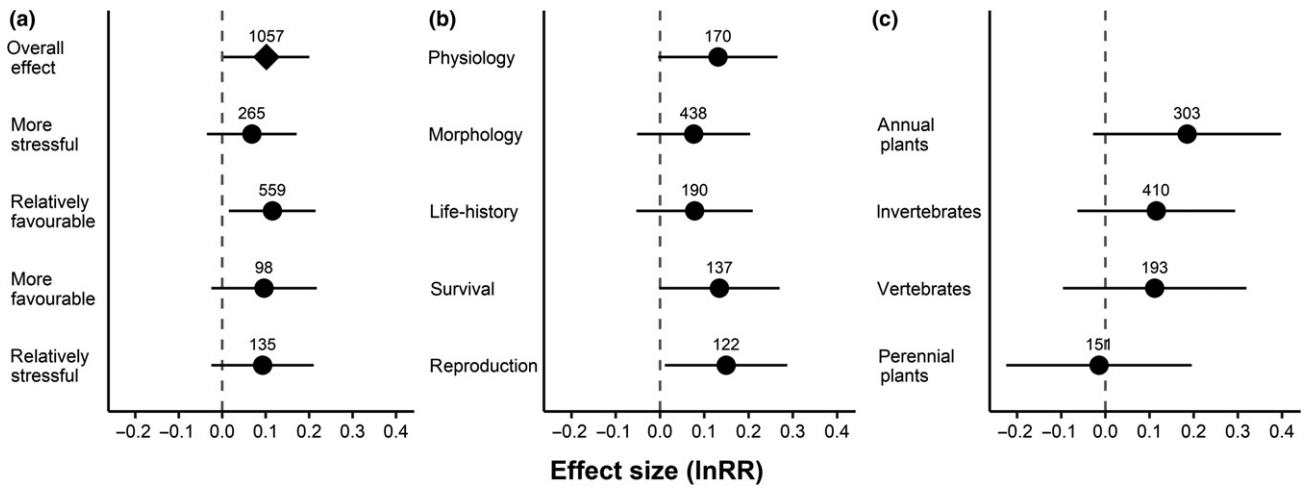
Figure 1 Results of the phylogenetic meta-analysis and three phylogenetic meta-regressions: (a) the overall effect and the effect in each environmental context, (b) the effect for each trait category and (c) the effect for each major taxonomic group. Overall, offspring do, on average, better in environments that match those of their ancestors, however, the 95% confidence intervals of those estimates are large, and often overlap with zero, in contrast to Yin *et al.* (2019). Points represent means, and error bars show the 95% confidence intervals. Numbers of contributing effect sizes are placed above point estimates.
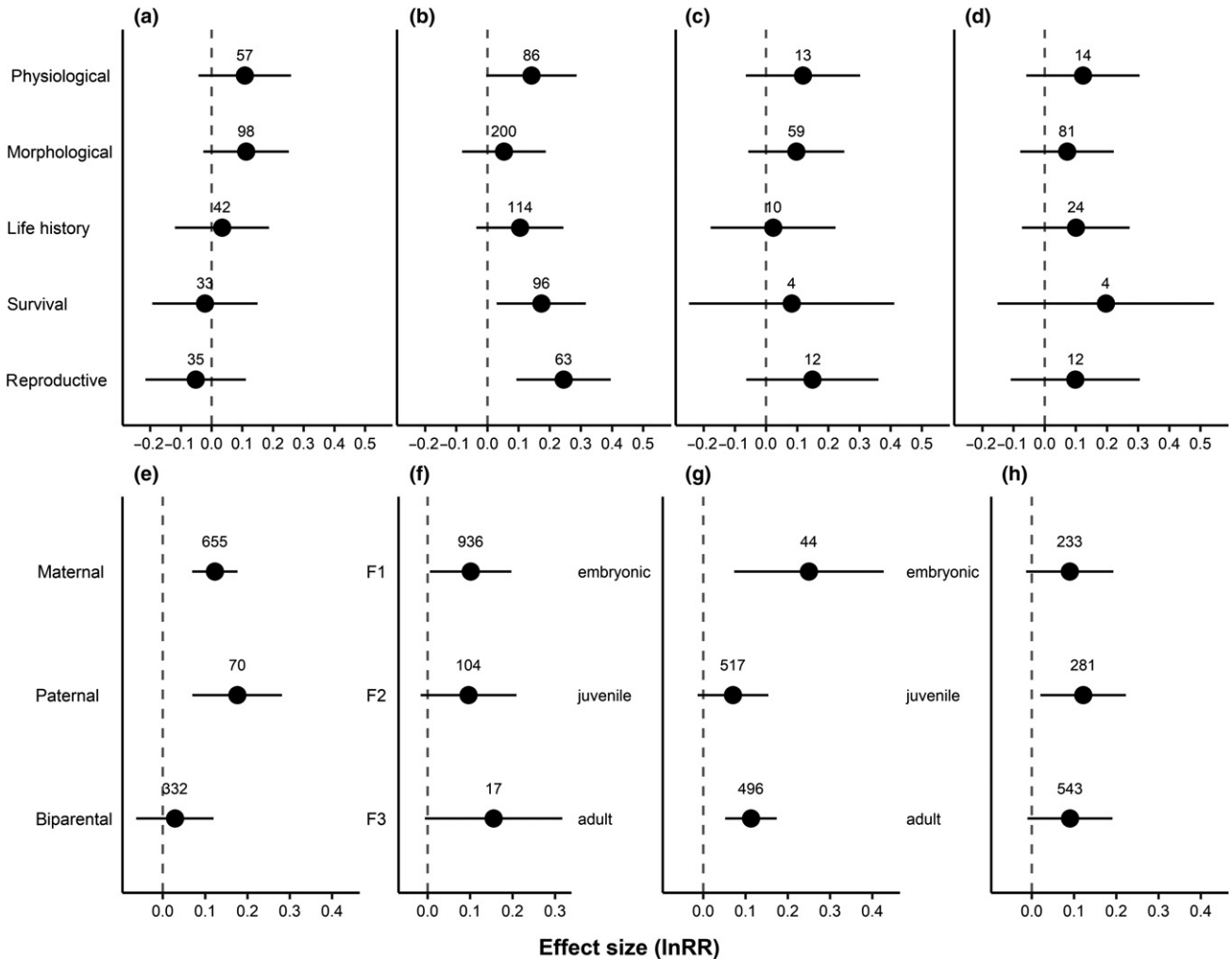

Figure 2 Results of a phylogenetic meta-regression testing the effect for each trait in each environmental context: (a) Env i: more stressful, (b) Env ii: relatively favourable, (c) Env iii: more favourable and (d) Env iv: relatively stressful. In addition, the results of four phylogenetic meta-regressions testing the effect for different (e) transmission types, (f) offspring generations, (g) ancestor developmental stages at exposure and (h) offspring developmental stages at measurement are also shown. Points represent means, and error bars show the 95% confidence intervals. Numbers of contributing effect sizes are placed above point estimates.

phylogenetic non-independence is neglected). That is, off-spring showed around 11% increased performance on average in matched versus unmatched environments. However, heterogeneity in effects, which was not reported in Yin *et al.* (2019), is high. Prediction intervals, which incorporate heterogeneity (IntHout *et al.*, 2016), allow us to predict that the true effect size of 95% of future, similar studies should range from − 0.55 (*c.* 42% decrease) to 0.75 (*c.* 113% increase); predictions that remain virtually the same regardless of the statistical model used (Supporting Information 5.4), making the generality of Yin's et al. (2019) statements more questionable. Importantly, even when exploring moderators we obtained more uncertain results (Figs 1 and 2; Supporting Information 5). Additionally, contrary to conclusions made by Yin *et al.* (2019), we found evidence for publication bias ('small-study effect' = missing some low precision effect sizes; Supporting Information 5.6) raising additional concerns about the magnitude and robustness of the results. Finally, most effect sizes analysed referred to parental (i.e. intergenerational) effects (93.6%); thus, the resulting estimates provide little insight into truly transgenerational effects (6.4% of effect sizes, Supporting Information 2.10). Overall, our re-analysis provides a more nuanced interpretation of the data and suggests that adaptive 'transgenerational' effects are not as robust and widespread as stated in Yin *et al.* (2019).

Despite the importance of differentiating anticipatory from condition-transfer parental effects for understanding the evolutionary causes and consequences of transgenerational effects (Bonduriansky & Crean, 2018; Engqvist & Reinhold, 2016, 2018), Yin *et al.* (2019) provided no real progress on this front. Two sources of evidence point at comparatively large condition-transfer effects: (1) the effect on traits closely related to fitness (reproduction and survival) was overall absent in the most stressful environments, but positive in milder environments (Fig. 2a–d); (2) effects were stronger when ancestors were exposed during embryonic development (Fig. 2g), which supports recent findings in water fleas (Radersma *et al.*, 2018).

Overall, while we applaud the efforts of Yin *et al.* (2019) in their attempts to provide greater clarity on the role of adaptive transgenerational effects, we believe their conclusions are still premature. Most of the issues we raised should be considered when performing a meta-analysis (see step-by-step Supporting Information), and some (data and analysis) could have been also rectified at the peer review stage, if journals would encourage reviewers to review data and code, or even assign a reviewer specifically for that task. We here encourage Ecology Letters to be a leading journal in this respect.

AUTHORSHIP

AST: Conceptualisation, Data curation, Formal analysis, Methodology, Investigation, Project administration, Resources, Software, Validation, Visualisation, Writing – original draft; ML: Conceptualisation, Validation, Writing – review & editing; NPM: Validation, Software, Writing – review and editing; SN: Conceptualisation, Funding acquisition, Supervision, Writing – review and editing; DWAN: Conceptualisation, Software, Supervision, Writing – review and editing;

KR: Conceptualization, Funding acquisition, Supervision, Writing – review and editing.

DATA AVAILABILITY STATEMENT

All data and code are available at Zenodo (http://doi.org/10.5281/zenodo.3549539).

REFERENCES

Agrawal, A.A., Laforsch, C. & Tollrian, R. (1999). Transgenerational induction of defences in animals and plants. *Nature*, 401, 60–63. https://doi.org/10.1038/43425.

Bonduriansky, R. & Crean, A.J. (2018). What are parental condition-transfer effects and how can they be detected? *Methods Ecol. Evol.*, 9, 450–456. https://doi.org/10.1111/2041-210X.12848.

Chamberlain, S.A., Hovick, S.M., Dibble, C.J., Rasmussen, N.L., Allen, B.G.V., Maitner, B.S. et al. (2012). Does phylogeny matter? Assessing the impact of phylogenetic information in ecological meta-analysis. *Ecol. Lett.*, 15, 627–636. https://doi.org/10.1111/j.1461-0248.2012.01776.x.

Engqvist, L. & Reinhold, K. (2016). Adaptive trans-generational phenotypic plasticity and the lack of an experimental control in reciprocal match/mismatch experiments. *Methods Ecol. Evol.*, 7, 1482–1488. https://doi.org/10.1111/2041-210X.12618.

Engqvist, L. & Reinhold, K. (2018). Adaptive parental effects and how to estimate them: a comment to Bonduriansky and Crean. *Methods Ecol. Evol.*, 9, 457–459. https://doi.org/10.1111/2041-210X.12906.

Fox, C.W., Thakar, M.S. & Mousseau, T.A. (1997). Egg size plasticity in a seed beetle: an adaptive maternal effect. *Am. Nat.*, 149, 149–163.

Galloway, L.F. & Etterson, J.R. (2007). Transgenerational plasticity is adaptive in the wild. *Science*, 318, 1134–1136. https://doi.org/10.1126/science.1148766.

IntHout, J., Ioannidis, J.P.A., Rovers, M.M. & Goeman, J.J. (2016). Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open*, 6, e010247. https://doi.org/10.1136/bmjopen-2015-010247.

Lajeunesse, M.J. (2011). On the meta-analysis of response ratios for studies with correlated and multi-group designs. *Ecology*, 92, 2049–2055. https://doi.org/10.1890/11-0423.1.

Marshall, D.J. & Uller, T. (2007). When is a maternal effect adaptive? *Oikos*, 116, 1957–1963. https://doi.org/10.1111/j.2007.0030-1299.16203.x.

O'Dea, R.E., Noble, D.W.A., Johnson, S.L., Hesselson, D. & Nakagawa, S. (2016). The role of non-genetic inheritance in evolutionary rescue: epigenetic buffering, heritable bet hedging and epigenetic traps. *Environ. Epigenetics*, 2, https://doi.org/10.1093/eep/dvv014.

Perez, M.F. & Lehner, B. (2019). Intergenerational and transgenerational epigenetic inheritance in animals. *Nat. Cell Biol.*, 21, 143–151. https://doi.org/10.1038/s41556-018-0242-9.

Radersma, R., Hegg, A., Noble, D.W.A. & Uller, T. (2018). Timing of maternal exposure to toxic cyanobacteria and offspring fitness in Daphnia magna: Implications for the evolution of anticipatory maternal effects. *Ecol. Evol.*, 8, 12727–12736. https://doi.org/10.1002/ece3.4700.

Shea, N., Pen, I. & Uller, T. (2011). Three epigenetic information channels and their different roles in evolution. *J. Evol. Biol.*, 24, 1178–1187. https://doi.org/10.1111/j.1420-9101.2011.02235.x.

Tollrian, R. (1995). Predator-induced morphological defenses: Costs, life history shifts, and maternal effects in daphnia pulex. *Ecology*, 76, 1691–1705. https://doi.org/10.2307/1940703.

Uller, T. (2008). Developmental plasticity and the evolution of parental effects. *Trends Ecol. Evol.*, 23, 432–438. https://doi.org/10.1016/j.tree.2008.04.005.

Uller, T., Nakagawa, S. & English, S. (2013). Weak evidence for anticipatory parental effects in plants and animals. *J. Evol. Biol.*, 26, 2161–2170. https://doi.org/10.1111/jeb.12212.

Yin, J., Zhou, M., Lin, Z., Li, Q.Q. & Zhang, Y.-Y. (2019). Transgenerational effects benefit offspring across diverse environments: a meta-analysis in plants and animals. *Ecol. Lett.*, 22, 1976–1986. https://doi.org/10.1111/ele.13373.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.