Host-pathogen interactions under pressure: a systematic review and meta-analysis of stress-mediated effects on disease dynamics

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Abstract

Human activities have increased the intensity and frequency of natural stressors and created novel stressors, altering host-pathogen interactions, and changing the risk of emerging infectious diseases. Despite the ubiquity of such anthropogenic impacts, predicting the directionality of outcomes has proven challenging. Here, we conduct a systematic review and meta-analysis to determine the primary mechanisms through which stressors affect host-pathogen interactions and to evaluate the impacts stress has on host fitness (survival and fecundity) and pathogen infectivity (prevalence and intensity). We assessed 893 effect sizes from 71 host species (representing seven taxonomic groups) and 78 parasite taxa from 98 studies. We found that infected and uninfected hosts had similar sensitivity to stressors and that responses varied according to stressor type. Specifically, limited resources compromised host fecundity and decreased pathogen intensity, while abiotic environmental stressors (e.g., temperature and salinity) decreased host survivorship and increased pathogen intensity, and pollution increased mortality but decreased pathogen prevalence. We then used our meta-analysis results to develop Susceptible-Infected theoretical models to illustrate scenarios where infection rates are expected to increase or decrease in response to resource limitation or environmental stress gradients. Our results carry implications for conservation and disease emergence and reveal areas for future work.

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Abstract: Human activities have increased the intensity and frequency of natural stressors and created novel stressors, altering host-pathogen interactions, and changing the risk of emerging infectious diseases. Despite the ubiquity of such anthropogenic impacts, predicting the directionality of outcomes has proven challenging. Here, we conduct a systematic review and meta-analysis to determine the primary mechanisms through which stressors affect host-pathogen interactions and to evaluate the impacts stress has on host fitness (survival and fecundity) and pathogen infectivity (prevalence and intensity). We assessed 893 effect sizes from 71 host species (representing seven taxonomic groups) and 78 parasite taxa from 98 studies. We found that infected and uninfected hosts had similar sensitivity to stressors and that responses varied according to stressor type. Specifically, limited resources compromised host fecundity and decreased pathogen intensity, while abiotic environmental stressors (e.g., temperature and salinity) decreased host survivorship and increased pathogen intensity, and pollution increased mortality but decreased pathogen prevalence. We then used our meta-analysis results to develop Susceptible-Infected theoretical models to illustrate scenarios where infection rates are expected to increase or decrease in response to resource limitation or environmental stress gradients. Our results carry implications for conservation and disease emergence and reveal areas for future work.

INTRODUCTION

Human-induced environmental changes are altering the world at an unprecedented rate, threatening the persistence of many animal and plant species by modifying habitats and disrupting interactions between coevolved species (Barnosky *et al.* 2012). These changes underscore the importance of understanding how human actions impact parasite dynamics in wildlife populations, as organisms that cause disease are of concern to human and animal health, biodiversity conservation, and ecosystem structure and function (Jones *et al.*2008; Wiethoelter *et al.* 2015; Allen *et al.* 2017; Rohr*et al.* 2019; Gibb *et al.* 2020). However, given the complexity and ubiquity of anthropogenic impacts, teasing apart the effects of perturbations on disease dynamics has become a major challenge. A key to solving this challenge is identifying how human-induced stressors affect processes that mechanistically impact epidemiological dynamics, such as host survival and fecundity and pathogen infectivity (i.e., the ability of a pathogen to establish an infection and replicate in a host).

A fundamental prediction of epidemiological theory is that high host density promotes parasite spread (McCallum *et al.* 2001). Therefore, is it reasonable to assume that stressors that impede population growth, by reducing host survival and fecundity, will reduce pathogen transmission. On the other hand, parasite transmission also depends on behavioral and immunological traits of a host that influence the acquisition, proliferation, and dissemination of parasites, a series of processes often summarized as host competence (Barron *et al.*2015). However, hosts may become more competent under stressful conditions that erode immune response to pathogens (i.e., resource limitation or agrochemical exposure) (Knutie *et al.* 2017; Rohr*et al.* 2008). Finally, stressors can have indirect and direct effects on pathogens. Host condition is likely to shape pathogen fitness by mediating intra-host resource availability (a bottom-up effect) and host immune response (a top-down effect), as reviewed and modeled by Cressler *et al.* (2014). In addition, pollution and environmental conditions may also negatively affect pathogens, especially in free-living stages (Pietrock & Marcogliese 2003). Considering these three distinct mechanisms is imperative when examining stress-mediated effects on disease dynamics, given that they predict different outcomes.

Our work aims to synthesize the current understanding of how human-induced stressors affect disease dynamics and consider the implications of these stressors concerning mitigating disease emergence and threatened species population declines. Here we define stress as any change that causes any actual or perceived threat to the homeostasis of an organism, precluding it from controlling a fitness-critical variable (Del Giudice *et al.* 2018). We begin by reviewing the literature to assess the support of the primary mechanisms by which stressors may affect host-pathogen interactions: by altering 1. host density, 2. host defenses, and 3. pathogen infectivity. Further, we conduct a meta-analysis of studies where impacts of host fitness (host survival and fecundity) and pathogen prevalence and intensity have been evaluated under benign and stressful conditions (low resources, adverse environmental conditions, and pollution) for infected and uninfected hosts. Given that host defenses and pathogen infectivity are rarely evaluated independently, we use infection prevalence and intensity to capture these two processes (hereafter infectivity). Specifically, we evaluated how the different types of stressors affect host fitness and pathogen infectivity, if fitness effects of stressors are more severe for infected vs. uninfected hosts, and if infectivity traits are more susceptible to stress than host fitness traits.

To further synthesize our results, we incorporate our empirical findings into two theoretical Susceptible-Infected (SI) models to elucidate scenarios where infection rates are expected to increase or decrease in response to the simultaneous trait changes occurring over resource and environmental stress gradients. Our meta-analysis' results support similarly negative responses of infected and uninfected hosts to stressors and identify stressor type as determinants for infection outcomes. Our results provide insights for predicting and mitigating the impacts of stressor-pathogen interactions on human and animal health, more relevant than ever, as human-induced perturbations are a growing threat worldwide.

MECHANISTIC LINKS BETWEEN STRESSORS AND PATHOGEN TRANSMISSION

Stressors modulate host density

A key assumption of many infectious disease models is that contact rates between infected and uninfected individuals increase as population density increases (Anderson *et al.* 1986; McCallum *et al.*2001). Therefore, if stressors depress host population growth, via reduced fecundity, increased mortality, or emigration, pathogens will be less frequently transmitted, and prevalence is expected to decline. This reasoning justifies culling campaigns, where infection rates are reduced, or pathogens are extirpated by reducing host density below a critical transmission threshold (Lafferty & Holt 2003). For example, population control of badgers (*Meles meles*) in the UK decreased bovine tuberculosis infection rates (Donnelly *et al.* 2007). However, culling campaigns have also backfired (Prentice *et al.*2019), like vampire bats (*Desmodus rotundus*) and rabies virus. Rather than targeting naïve susceptible individuals, bat culling efforts reduced the number of recovered seroconverted individuals and surviving individuals spread rabies to new bat colonies (Streicker *et al.*2012). Such examples demonstrate that a simplistic approach (e.g., reducing population density) may not necessarily yield intended results if other dynamic properties of wild populations are not considered (e.g., susceptibility to infections and animal movements).

Alternatively, stressors may contribute to increased local host density without increasing fecundity. For instance, behavioral responses to stressors, such as changes in migration patterns (Satterfield *et al.* 2018; Sánchez *et al.* 2020), foraging behaviors (Epstein*et al.* 2006), and aggregations in low-quality food-provisioned sites (intentional or unintentional) (Becker *et al.* 2015), have been associated with increased host density. Consequently, higher local density may intensify disease transmission via increased contact rates, as illustrated by theoretical models (Becker & Hall 2014).

Finally, stressors may affect the fitness of infected and uninfected hosts differently. It has been shown that infection increases sensitivity to other stressors, possibly because infected hosts are more energetically constrained (Marcogliese & Pietrock 2011). Such a combined effect of stress (i.e., climate change) and infection (i.e., chytrid fungus) may be responsible for the rapid global amphibian decline (Hof *et al.* 2011). Despite the many examples of the synergistic toll that stressors and pathogens have on host fitness, few efforts have tested whether such stressors have a differential impact on the fitness of infected compared to uninfected hosts (Marcogliese & Pietrock 2011; Beldomenico & Begon 2016).

Stressors constrain host defenses

Hosts invest resources to defend themselves from pathogens by resisting infections or tolerating disease (Råberg *et al.* 2007, 2009; Svensson & Råberg 2010). Resistance mechanisms control parasite growth and reproduction, reducing infection intensity, while tolerance reduces or compensates for infection-induced pathology without reducing pathogen burden (Boots 2008; Medzhitov *et al.* 2012). Although the two strategies have different disease implications, both have high energetic requirements (Ayres & Schneider 2009; Cumnock *et al.* 2018). Consequently, trade-offs exist between immune response and other energetically costly physiological processes, such as reproduction and growth (Lochmiller & Deerenberg 2000), in both vertebrates (Gustafsson*et al.* 1994) and invertebrates (Schwenke *et al.* 2016). Induction of an immune response, even without a pathogen, shows similar results (Demas 2004). Furthermore, there is recent evidence that trade-offs between reproduction and immune function exist at the transcriptomic level and may be conserved across animals (Rodrigues*et al.* 2021).

Given these trade-offs, it follows that under stressful conditions, hosts might not be able to defend themselves optimally from pathogens (Sheldon & Verhulst 1996; Gervasi *et al.* 2015). For instance, malnutrition can impair immune function by reducing T-cell-mediated immune response (Alonso-Alvarez & Tella 2001), toxicants can immunocompromise a host (Caren 1981) or upregulate host immunity (Pölkki*et al.* 2012), and extreme temperature variations can impair immunity leading to species declines (Rohr & Raffel 2010). Consequently, stressors can alter epidemiology through mechanisms that alter host susceptibility to infections. For example, Owen *et al* . (2021) showed that food-deprived robins (*Turdus migratorius*) developed higher West Nile Virus titers and were infectious longer than robins fed normally. Similarly, amphibians exposed to pesticides have experienced eosinophil recusation (a resistance mechanism) and associated increases in trematode infections and subsequent limb malformations (Kiesecker 2002). Conversely, the tolerance of Galapagos mockingbirds (*Mimus parvulus*) to infection has been impaired by climatically-induced food stress, exhibiting lower fledging success in dry years (when resources were scarce) compared to wet years, due to their inability to compensate for the cost of parasitic fly nest infestations (McNew *et al.* 2019).

Pathogens are affected by stressors as well

Pathogens can be affected by stressors directly or indirectly through their hosts. It is critical to distinguish these mechanisms, as each may affect host populations differently. By definition, pathogens rely on host resources to grow and reproduce (Casadevall & Pirofski 2002); therefore, pathogens compete for resources with host physiological processes that mediate disease outcome (i.e., reproduction, growth, immune defense; Cressler *et al.* 2014). Direct manipulation of immune response by pathogens has been documented (Maizels & Yazdanbakhsh 2003; Schmid-Hempel 2008), but pathogens may also outcompete host immune response by direct resource consumption (Cressler*et al.* 2014). For example, in a *Daphnia* -fungal parasite system, more resources could mean greater epidemics, not only due to an increase in *Daphnia* reproductive rates (i.e., host density driven) but also due to increased pathogen intensity within the host (Civitello *et al.* 2015).

On the other hand, a common sickness behavior, reduced food consumption, may be an adaptive host response (Murray & Murray 1979; Exton 1997; Ayres & Schneider 2009). Parasite-mediated anorexia can improve host health and recovery (Wang *et al.* 2016), much like fever (Kluger*et al.* 1996). Anorexia appears to intensify with higher levels of parasite exposure or intensity (as reviewed by Hite et al. (2020)). However, the advantages or disadvantages of anorexia depend on nutrient stores and quality, and ambient conditions (McKenzie & Townsend 2007; Johnson *et al.* 2010; Becker *et al.* 2015; Hite *et al.* 2020). Sometimes, a low-quality resource may be inadequate for the host while sufficient for the pathogen (Dallas & Drake 2014) or lead to fewer resources for the parasite (Kyriazakia *et al.* 1998; Hall*et al.* 2009b, a). Conversely, hosts may increase food intake to compensate for energy lost in fighting an infection (i.e., resource compensation hypothesis, (Christe *et al.* 1996)). As a result, high-resource diets could increase host tolerance to infections by reducing resource competition between hosts and parasites without negatively affecting parasite fitness (Knutie *et al.* 2017), with possible implications for the evolution of pathogen virulence (Hite*et al.* 2020).

Finally, pathogens may be directly impacted by environmental stressors, and in some cases, even more so than their host (Riggs *et al.*1987). Fluctuating environmental conditions and pollutants can negatively affect pathogens (Pietrock & Marcogliese 2003). For instance, deviations from temperature and salinity optima can reduce survival and lifespan in free-living helminths (Pechenik & Fried 1995; Measures 1996), and reduced longevity decreases the infective period. Similarly, elevated nitrate concentrations can reduce free-living spore survival, which may counteract the effects of increased intensity within*Daphnia* (Dallas and Drake 2014). Even when pathogens survive stressors, their capacity to infect hosts could be affected. For instance, metals can impact sensory receptors of environmental stages of parasites, such as cercariae, impairing their ability to locate, recognize and infect hosts (Ghandour & Webbe 1975; King & Higashi 1992; Morley *et al.* 2002).

META-ANALYSIS

We conducted a systematic review and meta-analysis to evaluate the impacts of three broad types of environmental stressors on disease dynamics. Our meta-analyses focused on two specific questions: Q1) are stressor fitness effects more severe for infected vs. uninfected hosts? and Q2) is infectivity more susceptible to environmental stress than host fitness traits? To address these questions with data from primary studies, we used infection intensity and prevalence as proxies for infectivity and survivorship and fecundity as proxies of host fitness.

Literature survey and study selection

To identify studies that evaluated the effects of environmental stressors on infectivity and host fitness traits in host-parasite systems, we conducted a systematic literature search in Web of Science using the search terms: (parasit* OR pathogen* OR disease) AND (environment* OR temperature OR pollution OR resource OR provision* OR toxi* OR contamination) AND (infection OR load OR yield OR resistance) AND ("birth rate" OR "death rate" OR surviv* OR mortality OR reproduct* OR fecundity). We limited our search to journal articles published in English between 2010 and 2020 and scanned titles and, if relevant, abstracts of all 20,684 hits. This initial screening was carried out by two experienced reviewers working independently. In addition, we identified ten more studies from the references of the selected studies. One experienced reviewer or two student reviewers further examined articles documenting effects of environmental stressors on infectivity and host fitness.

We classified stressors into three groups: 1) environmental factors, which can vary naturally but are also subject to human-induced perturbation (hereafter "endogenous environment"); 2) presence or quantity of chemical pollutants (hereafter "chemical pollution"), that lead to negative expected outcomes for hosts; and 3) resource availability for hosts (hereafter "resource limitation"). We excluded studies in which stressful and control environments differed by the presence of additional antagonistic biotic interactions (e.g., the presence of predators or competitors) or by the presence of substances purposely used as therapeutic interventions on infected hosts (e.g., chlorine added to water as a treatment against ectoparasites). Furthermore, we limited our search to studies with animal hosts and excluded studies on parasitoid infections (Fig. 1).

We included only experimental studies with hosts exposed to or infected by parasites under laboratory

conditions. Infected hosts were either exposed to pathogens or infected in laboratory settings. Yet, they could have cleared the infection during the experiment and had undetectable pathogen loads by the time fitness traits were quantified. We included studies only if infected hosts were exposed to stressful and control treatments and if the authors reported data of both host fitness (fecundity and/or survivorship) and pathogen infectivity (prevalence and/or intensity) from the same experiment (i.e., for the same pool of individuals divided between stressful and control treatments) at matched timepoint(s) (Fig. 1). For example, if a study reported infection intensity at 24 h and 72 h post-infection (hpi), but survivorship was only recorded at 72 hpi, we used the 72h data exclusively. If a study recorded both fitness and infectivity at multiple time intervals, we included all matched intervals in data collection. We accounted for the non-independence of these effects and their sampling errors in the random structure of our statistical models (see below). We excluded studies in which parasite shedding was recorded as a proxy for infection intensity. Studies were further excluded for pseudoreplication, missing sample size information, or when estimates were reported without associated errors (Fig. 1).

Data collection and transformations

We obtained primary literature data directly from the main text, tables, supporting material, or raw data files whenever available. Otherwise, we digitized data from figures using PlotDigitizer (https://plotdigitizer.com). Stressor effects were standardized to unbiased mean differences (Hedge's g) from both continuous and discrete variables (Hedges 1981). For continuous variables, we sought to obtain the mean and standard deviation (SD) of fitness traits and infectivity metrics in environments with different exposure to stressors. If SD was not reported, an error estimate (standard error (SE), 95% confidence interval (CI) or Wald's CI) was converted to SD, assuming normality. If a study reported the median instead of the mean (n = 13 effects in four studies), we estimated the mean following Hozo et al. (2005) If dispersion was only reported as data range or interquartile range (n = 8 effects in one study and n = 5 effects in three studies, respectively), we approximated SD (Lajeunesse 2013; Wan*et al.* 2014). The mean and SD of response variables were then used to calculate standardized mean differences (d) and their variances.

Many studies (n = 67) used discrete variables to quantify infection prevalence and/or survivorship. In these cases, we calculated odds ratios between environmental treatments and estimated their variances (Rosenberg *et al.* 2013). Also, in cases where at least one of the categories had no observations (e.g., no survival in the polluted treatment), we applied Yate's continuity correction to avoid dividing by zero (Yates 1934). Log odds ratios were then converted to d , and the variances of log odds ratios were converted to variances of$d$, assuming that a continuous logistic distribution underlies each discrete trait (Hasselblad & Hedges 1995). Finally, we estimated Hedge's g and its variance by applying the sample size correction$J$ to all values of d and their variances (Hedges 1981).

Most experiments (n = 108) contrasted host fitness traits and infectivity across three or more environmental treatments or in more than one-time interval. For example, a control group could be compared to two levels of chemical pollution or at both 24 and 48 hpi. In these cases, the stressor effects and sampling errors are not independent, as they were estimated against the same control group or time baseline. To account for correlated sampling errors between these effects, we computed covariances in sampling errors between effects in multiple-comparison designs following Viechtbauer (2010) and included these variance-covariance matrices in our statistical analyses (see below). In a few experiments (n = 8), large covariances between effects and small sample sizes resulted in variance-covariance matrices with negative eigenvalues, which were therefore not positive definite. We dealt with this issue by adjusting these covariance estimates to produce the nearest positive definite matrix using the R package *Matrix*(Douglas & Maechler 2021). As an alternative approach to estimating sampling error covariances, we adjusted fixed effect coefficients using the robust variance estimator (RVE) (Hedges *et al.* 2010), as implemented in the R package *clubSandwich* (Pustejovsky 2020). Here, we focus on the results with the estimated covariances and show the results under the RVE in the Supporting Material.

Moderators

We examined three factors that could moderate the magnitude of stressor effects. For Q1, we considered infection status (infected and uninfected), stressor type, and response trait (fecundity and survivorship) as moderators. Here, we were specifically interested in whether infection status amplified any negative fitness consequences of stressors. As mentioned above, stressors were of three types: 1) endogenous environmental factors, such as temperature, humidity, salinity, dissolved oxygen, habitat structural complexity, etc., 2) chemical pollution by toxins or synthetic compounds typically derived from pesticides or herbicides, and 3) resource limitation, primarily by restricting access to food but also included limitation of specific nutrients in food items, such as nitrogen and phosphorus. For response traits, fecundity was typically recorded as the total number of offspring, whereas survivorship was reported as proportion alive, number alive, and sometimes, time to death.

In Q2, we focused exclusively on infected individuals under the abovementioned criteria. We investigated stressor type and response trait as moderators. Here, we aimed to contrast the effects of stress on fitness vs. infectivity responses. We, therefore, included two additional response traits as infectivity proxies: infection intensity and prevalence. Prevalence was always reported as the number or percentage of infected individuals. Infection intensity was often quantified in different ways for different types of pathogens, for example, (log) copy number for viruses, colony-forming units for bacteria, and spore counts for fungi. To compare the relative sensitivity of fitness and infectivity, and because prevalence and infection intensity represents the opposite of host defense, signs of unbiased standardized mean differences were flipped. By doing so, a positive effect size reflects greater defense and a beneficial outcome for hosts, whereas for fitness traits, a positive sign indicates higher survivorship or fecundity.

Meta-analyses

We analyzed effect sizes (Hedge's g) for both Q1 and Q2 with multi-level meta-analytic (MLMA) models, fitted in R v 4.1.2 (R Core Team 2021) and using the package *metafor* version 3.0-2 (Viechtbauer 2010). We employed a model selection approach based on the Akaike Information Criterion (AIC) to identify the most important moderators explaining heterogeneity in effect sizes and the most parsimonious model (Arnold 2010). This required first fitting the full model and all reduced models via maximum likelihood (ML) estimation. For Q1, the full model included the moderator variables infection status, fitness trait, stressor type, and all their interactions. The full model for Q2 included response trait, stressor type, and their interaction.

All models accounted for the non-independence of effects and sampling errors measured in the same experiment. All models also included observation-level random intercepts, so residual variation within studies could be estimated. Full and reduced models (including the intercept-only model) were compared using the 'dredge' function of the R package *MuMIn* v 1.43.17 (Bartón 2020). The highest-ranking model based on the small sample size corrected AIC (AICc) was then refitted via restricted maximum-likelihood (REML) estimation to interpret moderators and evaluate publication bias and heterogeneity.

We report meta-analytic mean estimates and 95% confidence intervals for the effects of moderators in the final models. Meta-analysis results were plotted using the R package *orchaRd* (Nakagawa *et al.*2021). We tested the significance of statistical contrasts between fitness and infectivity response variables in Q2 using Wald-type chi-square tests, computed with the function 'anova'.

Heterogeneity

We estimated the proportion of heterogeneity relative to sampling error (I^2; Higgins and Thompson 2002) and partitioned it into between-study heterogeneity and within-study heterogeneity (Nakagawa & Santos 2012). Current formulations of I^2do not accommodate sampling-error covariances for multivariate meta-analytic models. We, therefore, fitted simpler models with only the observation-level variances to estimate I^2. While this is not ideal, we note that the meta-analytic effects of moderators accounting for sampling-error covariances are robust to these simpler models after adjustment with the RVE (see Supporting Material).

Publication bias

Following Nakagawa et al. (2022), we relied on two complementary approaches to assess small study effects, which may result from publication bias. First, we visualized the relationship between effect sizes and precision (SE) using funnel plots. To do this, we re-fitted the selected models as random effect models and computed the residual effect sizes conditional on the experiment, the observation, and factor level, for those factors included as moderators in the main analyses. These conditional residuals have the advantage of taking some of the within-experiment non-independence into account, but they still make unlikely assumptions about sampling variances (Nakagawa *et al.*2022).

We, therefore, complemented the funnel plots with a two-step, modified Egger's test for multilevel meta-analysis (Nakagawa *et al.* 2022). In the first step of this test, the SE of effect sizes is included as the only moderator in a meta-regression with the same random effect structure as in our main MLMA analyses. A significant slope of this moderator means that studies with low precision tended to report either more negative or more positive effects than studies with higher precision. Therefore, if the SE slope is different from zero, the second step of the test is to fit a meta-regression with the variance of effect sizes as the only moderator. The intercept of this second meta-regression is then a more appropriate estimate of the overall meta-analytic effect (Stanley & Doucouliagos 2014). Because we uncovered evidence consistent with publication bias in Q1 and Q2, we tested the robustness of the meta-analytic effects of moderators by fitting a multi-level meta-regression (MLMR) with variance in addition to the moderators of interest for each question in our study (see Supporting Material).

Summary of literature survey

Our final data set included 98 studies and 893 effects (Fig. 1). While most studies reported the results from a single experiment, 21 studies included between two and four experiments, resulting in a total of 122 experiments. Host taxa included arthropods (n = 20 species), molluscs (n = 13 species), fish (n = 13 species), amphibians (n = 21 species), and a few other vertebrates (two bird species, one reptile, and one mammal). Parasite taxa comprised viruses (n = 37), bacteria (n = 14), fungi (n = 6), parasitic animals (n = 13), and other eukaryotes (n = 8).

Q1: Fitness effects of stressors on infected and uninfected hosts

The lowest AICc model for Q1 included stressor type, response trait, and their interaction as moderators (Table S1). Our data, therefore, does not support differential effects of environmental stressors between infected and uninfected hosts (Fig. S1). The interaction between stressor type and response trait resulted primarily from a relatively negative strong effect of resource limitation on fecundity (Table S2; Fig. 2) and a relatively negative strong effect of endogenous environmental stressors on survivorship (Table S2; Fig. 2). Pollution also negatively affected survivorship (Table S2; Fig. 2), but this effect was contingent on the results of low precision studies (see Evidence of publication bias below). These contrasting effects of the three stressor types are qualitatively similar if the RVE is used instead of modeling sampling-error covariances (Fig. S2). Differences in effect sizes both within ($I^2 = 40.46\%$) and between ($I^2 = 53.42\%$) experiments contributed to relatively high total heterogeneity ($I^2 = 93.88\%$).

Q2: Sensitivity of host fitness and infectivity responses to stress

We contrasted the fitness and infectivity effects of stressors on infected hosts. The full model, including stressor type, response trait, and their interaction, was also the model with the lowest AICc score (Table S3). In this model, the interaction arises not only due to the differential sensitivity of fecundity and survivorship responses to stressor type but also because the direction of infectivity responses only aligned with fitness responses in the case of endogenous environmental stressors (Table S4; Fig. 3). Perturbation of the endogenous environment tended to have negative consequences for hosts, both in terms of survival and pathogen intensity (Table S4; Fig. 3, all infectivity vs. fitness contrasts $p > 0.05$; however, survivorship vs. prevalence: $p = 0.057$). In contrast, the effects of resource limitation differed significantly between response variables (fecundity vs. intensity: $p < 0.001$; fecundity vs. prevalence: $p = 0.006$; survivorship vs. infection intensity: $p = 0.010$; and survivorship vs. prevalence: $p > 0.05$). When resources were limited, not only was host fecundity reduced (as noted in Q1), but infection intensity was also reduced (Table S4; Fig. 3). Finally, the effects of chemical

pollution were more negative on survivorship than on either proxy of infectivity (survivorship vs. infection intensity: $p = 0.024$, survivorship vs. prevalence: $p = 0.018$). We found that pollution decreased both host survival and pathogen prevalence (Table S4).

We obtained a similar pattern of interaction among stressors and fitness and infectivity responses when the RVE was used to account for the non-independence of sampling errors (Fig. S3). Despite these contrasting effects of moderators, heterogeneity remained high (total $I^2 = 91.33\%$), both between ($I^2 = 55.86\%$) and within ($I^2 = 35.47\%$) experiments.

Evidence of publication bias

More negative effects of stressors in studies with lower precision suggested publication bias may partially explain our results for both Q1 and Q2 (Fig. 4). We confirmed these negative relationships between effect size and precision using a two-step modified Egger's test (Table S5). We thus adjusted meta-analytic estimates for the analyses in Q1 and Q2 by including variance as an additional moderator in both models.

Some of our results in Q1 differed qualitatively after adjusting for small study effects. Specifically, the effects of endogenous environmental stressors and pollution became non-significant when variance was included as a moderator (Table S6; Fig. S4). Moreover, the effect of resource limitation on survivorship changed direction after the small-study adjustment. However, we note that this effect was indistinguishable from zero in both unadjusted and adjusted models and was based on a few studies ($n = 8$).

In Q2, our qualitative results remained largely unchanged after adjusting for publication bias. Overall, the effects of endogenous environmental stressors reduced host survival and increased both infectivity traits (Table S7; Fig. S5). As in our primary analysis, resource limitation in the adjusted model negatively affected fecundity, but the meta-analytic effect on intensity was marginally non-significant (Table S7). Finally, adjusting for small-study effects revealed that the negative effects of chemical pollution on host survival and prevalence found in our primary analysis (Table S4; Fig. 3) became indistinguishable from zero in the adjusted model (Table S7; Fig. S5). However, we caution that this result was based on a relatively small number of experiments ($n = 9$).

INTEGRATING EMPIRICAL RESULTS INTO EPIDEMIOLOGICAL MODELS

When considering the effects of stress on infected host fitness and infectivity, we found that responses varied depending on the type of stressor. Environmental stress decreased host survivorship and increased infection intensity, pollution decreased host survival and pathogen prevalence, and limiting resources decreased host reproduction and pathogen intensity.

We integrated the best-supported relationships from our meta-analysis into mathematical models to evaluate the net impact of these simultaneous effects of stressors on host-pathogen interactions. We built two dynamic Susceptible-Infected (SI) models. An SI-Resource model following the framework of Civitello *et al.* (2018) where key processes (i.e., host reproduction and pathogen transmission) could depend on resource availability (Box 1). And an SI-Environmental gradient model following the framework of Lafferty & Holt (2003) where key processes (i.e., host survivorship and pathogen transmission) could depend on an abiotic environmental factor (Box 2). Because our meta-analysis suggested no proportional difference between uninfected and infected hosts for survival or reproduction, we incorporated this result by including a common parameter for the strength of these effects on both groups (Box 1 and Box 2).

We used the models to determine the equilibria of disease prevalence as a function of resource availability and environmental stress gradients, using the numerical integration function "lsoda" in the R package *deSolve* (Soetaert *et al.* 2010). We examine different scenarios in which fecundity and infectivity, or background death and infectivity, had different sensitivities to either resource (Box 1) or environmental stress gradients (Box 2), respectively. We simulated the epidemiological dynamics of each model across a gradient of either resource availability or environmental stress, then plotted the equilibrium infection prevalence and host density against such gradients for each model (Fig. 5).

Model predictions

Using our dynamical models (Box 1 and Box 2), we evaluated whether the patterns of trait sensitivity to stressors we documented in the meta-analysis reduce or increase infection prevalence across stress gradients and how stressors ultimately impact host population densities. The SI-Resource model predicts that a decrease in resource productivity decreases infection prevalence (Fig. 5A), in part because host densities also decrease with limited resources (Fig. 5C). Once a pathogen establishes in a population, there is stabilizing feedback, where pathogens suppress host density, increasing resources, and further increasing transmission. Therefore, in all scenarios of sensitivity of pathogen transmissibility to resources (smaller values of the half-saturation transmission constant (h_t) increase the sensitivity of transmission rate (β) to resources), the model reaches the same prevalence equilibrium. However, although population density also stabilizes, the impacts on host density are different for each scenario: populations that are more sensitive to resources available will reach smaller population sizes compared to less sensitive populations (Fig. 5C)

The SI-Environmental stress gradient models show that population density decreases regardless of the effects of stress on hosts susceptibility due to increased mortality. But it exponentially decreases host populations when transmission rate is sensitive to the environmental factor (Fig. 5B and D). Specifically, when stress increases host susceptibility (i.e., greater values of β_E), infection prevalence will increase rapidly (Fig. 5B) but at the cost of increasing host mortality (Fig. 5D). Therefore, infection prevalence will have a maximum at intermediate stress level but will drop as population densities are too low to sustain transmission. In contrast, as transmission is more negatively affected by stressors (i.e., pathogens are negatively affected by stressors), infection prevalence will quickly reach zero with increasing environmental stress (Fig. 5B). But as the stress increase and persist, populations will decline after the pathogen is extirpated from the system (Fig. 5D).

Our models illustrate that the consequences of stress gradients on disease can depend on the sensitivity that host traits, such as births and deaths, and shared host-pathogen traits, such as transmission (i.e., β) have to stressors. Interestingly, and consistent with Lafferty & Holt (2003) simulations, our models showed that increased environmental stress generally decreased disease, mainly driven by host density reductions. Although stress can make hosts more likely to become infected at the individual level, at the population level, negative impacts on host survival and reproduction may be driving pathogen and host local extinctions (Lafferty & Holt 2003).

DISCUSSION

Stressor type modulates host fitness and infectivity in different ways

Our meta-analysis documented the dominant effects of stressors on host fitness and pathogen infectivity. Interestingly, we found that infected and uninfected hosts had proportionally similar sensitivity to stressors regarding survival and fecundity. Furthermore, stressor type determined host fitness and pathogen infectivity outcomes. Although we found that resource limitation decreased host fecundity and pathogen intensity, other authors have described positive, negative, and unimodal relationships across animal taxa. For example, Cressler *et al.*(2014) found that as invertebrates increased their resource uptake, they increased their pathogen intensity, whereas increased resource consumption decreased pathogen intensity in vertebrates. They argued that this differential response could be due to their distinct immune systems and body sizes (Cressler *et al.* 2014). Contrary to their results, we found that both vertebrate and invertebrate hosts (which represented most of our data) reproduced less and carried a lower pathogen burden when facing limiting resources. One possible explanation is that hosts are investing resources in their immune defense mechanism at the cost of reproduction. In support of this hypothesis, it has been proposed that illness-mediated anorexia may enhance immune function by acting as a "master switch" that reduces the investment in other physiological processes (Hite *et al.* 2020). For example, Cumnock*et al.* (2018) showed that malaria-infected mice strongly reduced their food intake and switched their metabolism from burning sugar (glycolysis) to burning fats (ketosis), which influenced host tolerance to infections. Alternatively, resource limitations could negatively affect pathogens, decreasing their capacity to reproduce within hosts. A third explanation could be that hosts

under limited resources could be smaller, and small hosts may carry fewer pathogens, therefore decreasing pathogen intensity within host. This has been reported in the snail-Schistosome system, where smaller snails carry fewer parasites (Civitello *et al.* 2022). Moreover, in *Daphnia* populations, food shortage reduced body size with subsequent reductions in spore loads of a microsporidian parasite (Pulkkinen & Ebert 2004).

Regarding endogenous environmental stressors, we found that when hosts are stressed, they survive less but have higher pathogen intensity. Coping with fluctuating abiotic environments can be energetically demanding for hosts, and human activities may exacerbate the frequency and severity of naturally occurring fluctuations. For example, temperature variation occurs naturally, but climate change makes it unpredictable or more drastic (Harvell *et al.* 2002; Marcogliese 2008). It is likely that hosts barely persisting in an environment are not able to resist infections (increasing pathogen proliferation) and/or compensate for the damage done by the pathogen (tolerating infection). One of the most documented examples of this possible scenario is given by the amphibian-chytrid fungus system under the pressure of climate change, increasing their susceptibility to pathogen infections (Alford*et al.* 2007; Rollins-Smith *et al.* 2011).

Finally, we found that hosts exposed to pollutants increased their mortality but decreased pathogen prevalence. However, we note that these results must be interpreted cautiously, given that the experimental studies included in our meta-analysis intentionally use sub-lethal doses of toxins. Low prevalence may be due to hosts dying before replicating and transmitting the pathogen. This result is consistent with mechanistic models of how toxicants influence pathogen transmission showing that infection prevalence was lower in more contaminated landscapes due to high host mortality (Sánchez *et al.* 2020). Although pollution can decrease parasitism if infected hosts suffer more than uninfected hosts from pollutant exposure, our analysis showed that hosts are equally sensitive to toxins regardless of infection status. Alternatively, parasites could also be negatively affected by pollution. For example, Gheorgiu *et al.* (2006) studied the effects of zinc concentration on a fish-parasite system and showed that while mortality increases in infected hosts as zinc concentration increased, parasite burden peaked at intermediate zinc concentrations. A follow-up study revealed that both parasite lifespan and fecundity were also negatively affected by zinc (Gheorgiu *et al.* 2007).

Implications for biodiversity conservation and disease transmission

While there are many examples of human activities conspicuously causing wildlife population declines (Dirzo *et al.* 2014), more subtle disruptions of host-pathogen interactions can also significantly affect population dynamics. Take the example of the worldwide amphibian decline: although mass mortalities have been linked to chytrid fungus infections (Lötters *et al.* 2009), research shows that the pathogen is not a sufficient cause of ongoing declines (Alford *et al.* 2007; Rollins-Smith *et al.* 2011; Scheele *et al.*2019). Global warming, another culprit, also degrades amphibian's condition (Reading 2007), making them more susceptible to the fungus and potentially to other stressors (Garner *et al.* 2009; Rollins-Smith*et al.* 2011; Cohen *et al.* 2019a, b, 2020). In the wild, when pathogens are highly virulent, sick individuals are seldom found, probably due to reduced survivorship and diminished activity when ill. However, sick or dead individuals are conspicuous at infrequent times, such as in the beforementioned amphibian mass mortality events (Lötters*et al.* 2009). As sick animals become abundant, they could be more commonly detected, indicating an ongoing population decline (green lines in Fig. 5B and C) (Beldomenico & Begon 2016).

The effects of multiple stressors (e.g., environmental stressors plus infection) could lead to vicious cycles, where a host in poor condition might not respond adequately to infection, further reducing the condition and susceptibility to stressors and additional infections (Beldomenico & Begon 2016). If we consider multi-host pathogens, which are the majority of known pathogens (Woolhouse *et al.* 2001), those vicious cycles could have not only a negative effect at the population level but also at the community level (Beldomenico & Begon 2016). Considering multi-host pathogens, Lafferty & Holt (2003) showed a positive association between stress and disease because transmission did not decrease as a specific host population became rare (as in our models with a single species), posing a threat to the most vulnerable species and conservation.

Our findings also suggest negative implications for public health. Animals under stress could become more competent hosts (i.e., host ability to transmit pathogens to other hosts or vectors) as conditions deteriorate

(Gervasi *et al.* 2015). Changes in immunity can influence parasite spread by increasing per-contact transmission probabilities or lowering host recovery rates, extending the duration of the infectious period (Altizer *et al.* 2006). Consequently, increasing the probability of intra- and inter-species transmission and posing a risk for spillover to human and domesticated animal populations (Plowright *et al.* 2017). For example, nutritional stress has been identified as one of the main risk factors for Hendra virus infection in flying foxes (*Pteropus* sp.), leading to the spillover events that affected both livestock and humans (Plowright *et al.* 2015; Becker*et al.* 2022; Eby *et al.* 2023).

Future directions and concluding remarks

Our analysis included all experimental studies, with hosts exposed to a single parasite species and a single stressor. This approach, although easier to interpret and valuable to tease apart the effects of a stressor in host-pathogen interactions, is difficult to translate to the natural world, where populations are likely exposed to multiple parasites and a combination of stressors. When considering co-infections, for instance, stressors might compromise one arm of immune defense, making hosts more vulnerable to pathogens that require such response. For example, food restriction increased levels of eosinophils in capybaras (a Th2 immune response) and consequently reduced nematode burden (which resistance relies on the Th2 response), but coccidian infection intensity increased due to inadequate Th1 immune response (Eberhardt *et al.* 2013). Future studies should use a combination of field and laboratory experiments to perturb processes that covary with stressors to determine how and why results vary comparing laboratory and real-world conditions.

As a next level of complexity, host-pathogen systems do not occur in isolation, and some other biotic stressors and interactions can indirectly affect disease dynamics. For example, hosts compete for resources with other species and are consumed by predators. Consequently, stressors can affect other community members in ways that could enhance or negate epidemiological effects on hosts and pathogens (Strauss *et al.* 2015, 2016). Furthermore, most known parasites infect multiple host species (Woolhouse *et al.* 2001), but some host species are disproportionately responsible for parasite transmission (Haydon *et al.* 2002). Generally, ecologically resilient species exhibit fast life histories and invest relatively less in immune defense compared to more disturbance-sensitive species (Johnson *et al.* 2012; Previtali *et al.* 2012; Pap *et al.* 2015), predicting that resilient species will have an insufficient immune response to prevent pathogen replication and transmission, resulting in higher transmission rates. Therefore, future research is sorely needed to evaluate the effects stressors have on different host species and their relative contribution to community disease transmission.

Moreover, combining experimental and modeling approaches is needed to move beyond associational patterns and to a mechanistic understanding of how stressors affect hosts and pathogens due to the common occurrence of multiple simultaneous stressors. Approaches are available for incorporating stressors into epidemiological models, such as examining variation in R_0, the basic reproductive number of a parasite (Anderson & May 1991). Pinpointing when and how stressors increase or decrease R_0 represents a crucial first step toward understanding their roles in the dynamics of infectious diseases. Yet even though multiple mechanisms (including changes in host contact rates and per-contact probability of transmission) are often subsumed in the transmission parameter β, these need not be fixed, as we have illustrated with our models. The same applies to birth and death rates, and even to parasite virulence, given that variation in host immune defenses alters per-contact transmission probabilities and the duration of the infectious period. As a next step, integrating a series of models with empirical results will inform the generality of the predicted patterns.

Finally, our study also highlights the need to expand empirical research at the interface of stress and infectious disease in highly relevant systems for zoonotic disease emergence. The studies included in our meta-analysis had low coverage of both vertebrates and terrestrial systems, yet terrestrial vertebrates such as rodents and bats have been linked repeatedly to zoonotic diseases affecting humans and livestock (Luis *et al.* 2013; Han *et al.* 2016). However, only one study of rodents provided sufficient data to be included in our meta-analysis (Eze *et al.* 2013).

As anthropogenic activities continue to alter ecosystems in ways that facilitate disease emergence worldwide, we must consider the effects stressors have on disease dynamics. Our findings improve our understanding of

this interplay and provide insights for predicting and mitigating the impacts of stressor-pathogen synergies on human, animal, and planetary health.

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Conflict of interest

The authors declare no conflict of interest.

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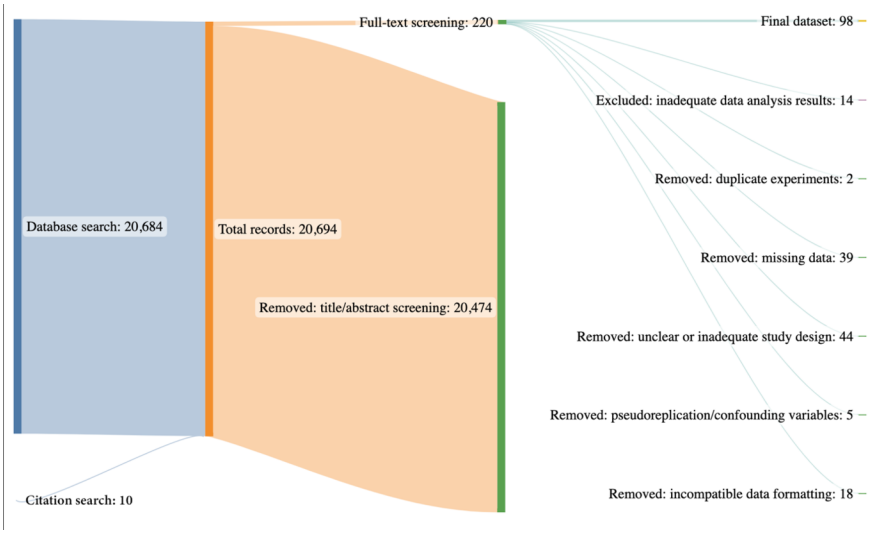

Figure 1. PRISMA diagram documenting our study screening for inclusion and exclusion for the meta-analysis. Each stage of the data collection process is highlighted with different colored pipes (blue: literature search; orange: title/abstract screening; green: full-text screening).

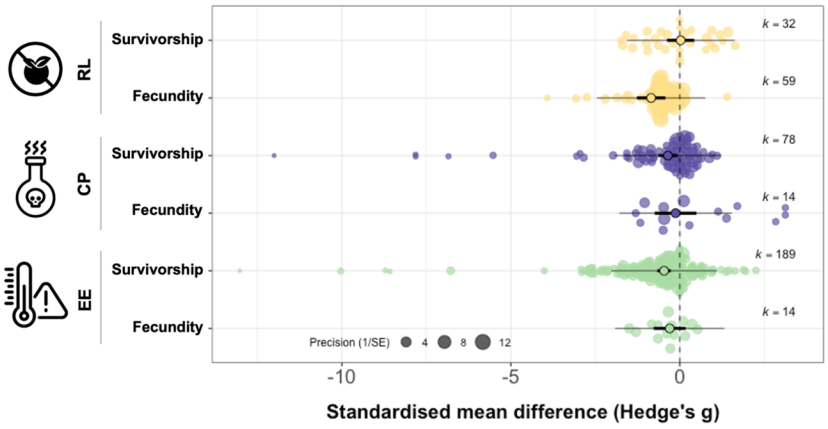

Figure 2. Orchard plot for the best multi-level meta-analytic (MLMA) model of the effects of environmental stressors on host fitness traits. The model includes two factorial moderators: stressor type, coded as "endogenous environment" (EE), "chemical pollution" (CP), and "resource limitation" (RL), and fitness response trait ("fecundity" or "survivorship"). Nodes in the same color show effects of the same stressor. The overall mean effect sizes (Hedge's g) for each combination of stressor and response trait are shown as circles with black border lines. 95% confidence intervals are represented by the thick black bars, and prediction intervals are represented by the thin bars. The number of effects for each category (k) is given in parentheses. Circle size is proportional to effect size precision.

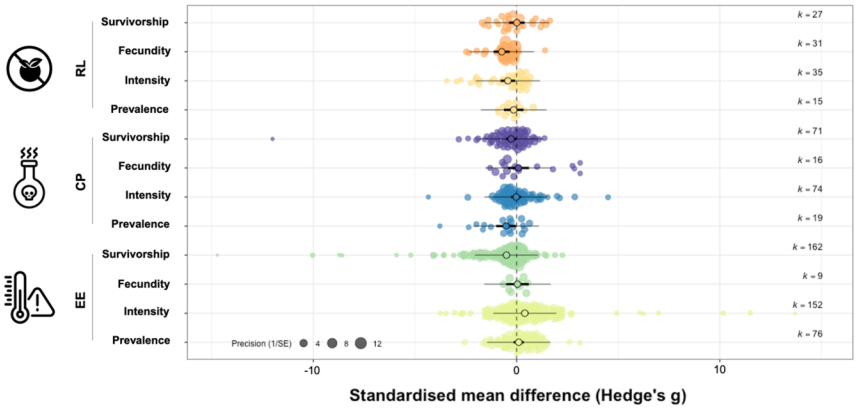

Figure 3. Orchard plot for the best multi-level meta-analytic (MLMA) model of the effects of environmental stressors on host fitness traits and infectivity. The model includes two factorial moderators: stressor type, coded as "endogenous environment" (EE), "chemical pollution" (CP), and "resource limitation" (RL), and response trait ("prevalence", "intensity", "fecundity" or "survivorship"). Negative effect sizes imply reduced fecundity, survivorship, infection prevalence, or intensity. Nodes in the same color show effects of the same stressor on the same category of the response variable (fitness or infectivity). The overall mean effect sizes (Hedge's g) for each combination of stressor and response variable are shown as circles with black border lines. 95% confidence intervals are represented by the thick black bars, and prediction intervals are represented by the thin bars. The number of effects for each category (k) is given in parentheses. Circle size is proportional to effect size precision.

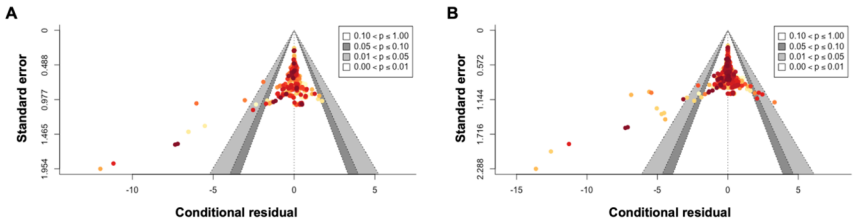

Figure 4 . Funnel plots showing the relation between precision (SE) and conditional residuals of the effects of environmental stressors on A) fitness and B) fitness and infectivity responses in animal hosts. Dark and light grey areas show bounds of 90% and 95% CIs for conditional residuals given the SE. Circles represent individual effects and are colored by precision, with dark red representing greater precision.

Box 1. SI-Resource model Susceptible (S) and infected hosts (I) are foraging on available resources (R), while resources

Box 2. SI- Environmental stress gradient model Susceptible hosts (S) grow logistically and have a density at which b

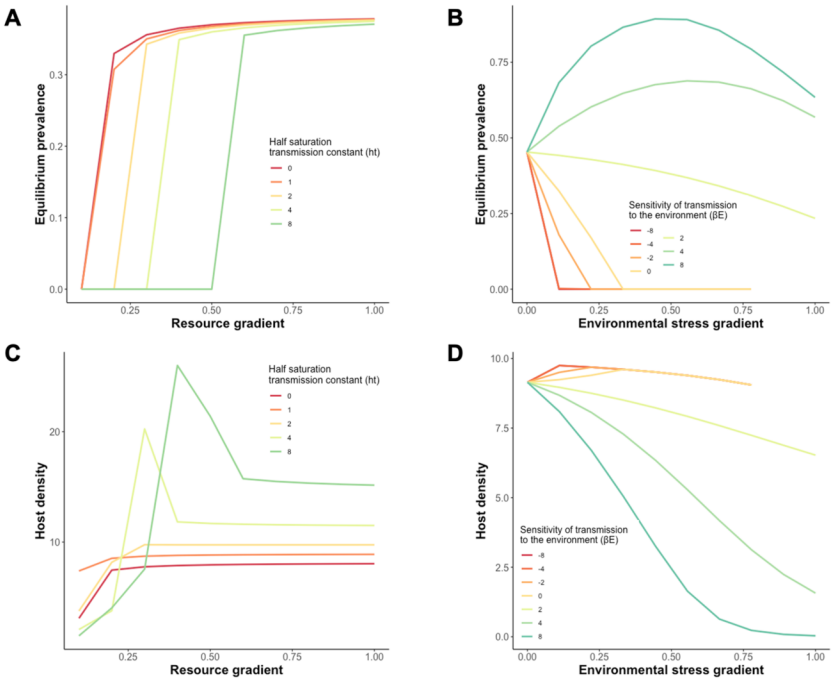

Figure 5. Contrasting outcomes for equilibrium prevalence (A and B) and host density (C and D) from hypothetical epidemiological models that illustrate dynamics that rise when fitness traits (survival and fecundity) and infectivity (transmission rate) vary with stressors, as demonstrated by our meta-analysis results. A and C are simulation outcomes of SI-Resource model. The half-saturation transmission constant (h_t) determines the transmission rate (β) response to resource availability, where a greater value of h_t makes the β less sensible to resources, and vice versa. B and D are simulation outcomes of SI-Environmental stress model. In the model, β could have different sensitivities to environmental factors (β_E), ranging from positive to negative. For parameters used in each model simulation, see Box 1 and 2, respectively.