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

Amanda Vicente-Santos[1], Beatriz Willink[2], Kacy Nowak[3], David Civitello[1], and Thomas Gillespie[1]

[1]Emory University
[2]Stockholm University
[3]Emory University School of Public Health

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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 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 891 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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Amanda Vicente-Santos[1*], Beatriz Willink[2,3,4], Kacy Nowak[5], David J. Civitello[1,6], and Thomas R. Gillespie[1,5,7*]

[1]Population Biology, Ecology, and Evolution Program, Emory University, Atlanta, GA 30322, USA

[2]Department of Zoology, Stockholm University, Stockholm 106-91, Sweden

[3]Department of Biological Sciences, National University of Singapore, Singapore 117558, Singapore

[4]School of Biology, University of Costa Rica, San José 11501-2060, Costa Rica

[5]Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, GA 30322, USA

[6] Department of Biology, Emory University, Atlanta, GA 30322, USA

[7]Department of Environmental Sciences, Emory University, Atlanta, GA 30322, USA

*Correspondence: Amanda Vicente-Santos. Sutton Hall 107, Biology Department, University of Oklahoma, Norman, OK 73019, USA amanda.vicente@ou.edu Tel. +1(404) 276-9990; and

Thomas R. Gillespie. 400 Dowman Drive, Suite E510, Department of Environmental Sciences, Emory University, Atlanta, GA 30322, USA thomas.gillespie@emory.edu Tel: +1(404) 727-7926

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Email addresses:amanda.vicente@ou.edu, beatriz.willink@zoologi.su.se, kkacy.nnowak@gmail.com, david.james.civitello@emory.edu, thomas.gillespie@emory.edu

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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 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 891 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

Accelerating anthropogenic impacts are modifying habitats and disrupting interactions between coevolved species (Barnosky *et al.* 2012), including host-pathogen dynamics, raising concern for 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 proven difficult. 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).

Stressors affect transmission dynamics in three fundamental mechanistic ways. First, when stressors reduce host survival and fecundity, they reduce host density, and by extension, transmission of density-dependent pathogens (McCallum *et al.* 2001). Second, host behavioral and immunological traits that influence the

acquisition, proliferation, and dissemination of pathogens, a series of processes often summarized as host competence (Barron *et al.* 2015). Host competence may increase under stressful conditions that erode immune response to pathogens (resource limitation or agrochemical exposure) (Knutie*et al.* 2017; Rohr *et al.* 2008). Third, stressors can have direct and indirect effects on pathogens. Host condition can shape pathogen fitness by mediating intra-host resource availability and host immune response, as reviewed and modeled by Cressler *et al.*(2014). Pollution and environmental conditions may also negatively affect pathogens, especially in free-living stages (Pietrock & Marcogliese 2003). Given that these three distinct mechanisms predict different outcomes, it is imperative to consider them collectively when examining stress-mediated effects on disease dynamics.

We aim to synthesize the current understanding of how human-induced stressors affect disease dynamics and consider the implications of these stressors for mitigating disease emergence and threatened species population declines. Here we define stress as any change that causes actual or perceived threats to the homeostasis of an organism (pathogen or host), precluding it from controlling fitness-critical variables (Del Giudice *et al.* 2018). We began by reviewing the literature to assess how stressors may affect host-pathogen interactions by altering (1) host density, (2) host defenses, and (3) pathogen infectivity. Further, we conducted a systematic search and meta-analysis of studies where 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 used infection prevalence and intensity to capture these two processes (hereafter infectivity). Specifically, we evaluated how different types of stressors affected host fitness and pathogen infectivity, if fitness effects of stressors were more severe for infected vs. uninfected hosts, and whether infectivity traits were more susceptible to stress than host fitness traits.

To further synthesize our results, we incorporated our empirical findings into two theoretical Susceptible-Infected (SI) models to elucidate scenarios where infection rates were expected to increase or decrease in response to the simultaneous trait changes (i.e., host fitness and pathogen infectivity) occurring over resource and environmental stress gradients. Our meta-analysis revealed similarly negative responses of infected and uninfected hosts to stressors and identified stressor type as determinant of 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 negatively impact host fitness by restricting host population growth via reduced fecundity or 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; Prentice *et al.* 2019). Although, to our knowledge, no studies have explicitly evaluated the stressor-density-disease relationship, studies have shown that human pressures indirectly increase host-density thresholds resulting in epidemics. For instance, overfishing of predatory lobsters (*Panulirus interruptus*) has led to dense purple urchin (*Strongylocentrotus purpuratus*) populations, more likely to experience urchin-specific bacterial (*Vibrio* bacteria) epidemics (Lafferty 2004). Similarly, although thermal stress increases the susceptibility of corals to disease, it only leads to white syndrome outbreaks where corals are at high density (Bruno *et al.* 2007).

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 higher host density. Con-

sequently, higher local density may intensify disease transmission via increased contact rates, as illustrated by theoretical models (Becker & Hall 2014).

Disease transmission can also be sustained at low population density. For instance, in social species, the frequency of social contact can govern disease epidemics independently of host density (Johnson *et al.* 2011; Rimbach *et al.* 2015; Rushmore *et al.* 2017). Given that density-independent transmission (e.g., sexual or vector-borne transmission) does not require a minimum host density for parasites to invade a population (Hopkins *et al.* 2020), it is expected that a combination of stressors and pathogen infection would drive populations to extinction more frequently than density-dependent transmissions (Castro *et al.* 2005; Ryder *et al.* 2007).

Stressors may affect the fitness of infected and uninfected hosts differently. Infection increases sensitivity to other stressors, as infected hosts are more energetically constrained (Marcogliese & Pietrock 2011). Such a combined effect of stress (warming temperatures) and infection (e.g., *Vibrio coralliilyticus*) may be responsible for the rapid global coral reef decline (Maynard *et al.* 2015). Despite many examples of synergistic tolls that stressors and pathogens have on host fitness (Crain *et al.* 2008), few have tested whether 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 via behavioral or physiological mechanisms. While avoidance behavior is less understood (Buck *et al.* 2018), physiological mechanisms, such as infection resistance or disease tolerance, are well documented (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 resistance limits pathogen replication while tolerance does not, leading to different disease implications (Schneider & Ayres 2008), both strategies have high energetic requirements, and hosts should only elicit them if parasite infections reduce their fitness (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). 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, host defense may be compromised under stressful conditions (Sheldon & Verhulst 1996; Gervasi *et al.* 2015).

Stressors may modulate host defensive mechanisms against infections. 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 variation can impair immunity leading to species declines (Rohr & Raffel 2010). 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, infection tolerance in Galapagos mockingbirds (*Mimus parvulus*) 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 inability to compensate for costs of parasitic fly nest infestations (McNew *et al.* 2019). These examples show that host susceptibility to infections and/or pathogen transmission may increase under stressful conditions.

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 equate to greater epidemics due to both higher*Daphnia* reproductive rates (i.e., host density driven) and higher infection intensity (Civitello *et al.* 2015), suggesting that food stress lowers parasitism in the *Daphnia* -fungal parasite system.

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.* 2009a, b). Conversely, hosts may increase food intake to compensate for energy lost fighting infections (i.e., resource compensation hypothesis (Christe *et al.* 1996)). As a result, high-resource diets may 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).

Environmental stressors may also directly impact pathogens with environmental stages (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 infective periods. 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).

Finally, differential effects of stressors on directly vs. indirectly transmitted pathogens (i.e., vector-borne or intermediate hosts) may lead to divergent outcomes (Hopkins *et al.* 2020). For instance, Studer *et al.* (2010) showed that although increased temperatures favored the development of the trematode *Maritrema novaezealandensis* within their intermediate amphipod host,*Paracalliope novizealandiae* , warmer temperatures increased amphipod mortality, creating a bottleneck for pathogen transmission. Similarly, qualitative differences between aquatic and terrestrial systems, due to life history differences and the greater taxonomic diversity of aquatic parasites and hosts (Harvell *et al.* 2002; McCallum *et al.* 2004; Byers 2021), may result in divergent disease outcomes. For example, environmental transmission dominates aquatic systems (Lafferty 2017), making pathogens more susceptible to direct effects of stressors.

META-ANALYSIS

We conducted a systematic literature search and meta-analysis to evaluate the impacts of three broad types of environmental stressors on disease dynamics. First, we confirmed that pathogen exposure in laboratory studies typically negatively affected host fitness. We then proceeded with our main meta-analyses focused on two specific questions: Q1) were stressor fitness effects more severe for infected vs. uninfected hosts?, and Q2) was 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, on February 9th of 2021, 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 effort was split and carried out by two experienced independent reviewers (AVS and BW). We identified ten additional studies from references of 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"). Although, in natural systems, these stressors often overlap (e.g., increased temperature can alter resource availability), we included studies where only one stressor was evaluated to facilitate the interpretations of our results. We excluded studies if stressful and control environments differed due to additional antagonistic biotic interactions (e.g., presence of predators or competitors) or by the presence of substances purposely used as therapeutic interventions on infected hosts (e.g., chlorine as water treatment). 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. We only included studies if infected hosts were exposed to stressful and control treatments and both host fitness (fecundity and/or survivorship) and pathogen infectivity (prevalence and/or intensity) were reported from the same experiment (i.e., 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 72h data. If a study recorded both fitness and infectivity at multiple time intervals, we included all matched intervals in data collection. We accounted for non-independence of these effects and their sampling errors in the random structure of our statistical models (see sections*Meta-analyses* and *Publication bias*). 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 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 obtained 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 median instead of 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). 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 variances (Rosenberg *et al.* 2013). In cases where at least one category had no observations (e.g., no survival in polluted treatment), we applied Yate's continuity correction to avoid dividing by zero (Yates 1934). Log odds ratios were then converted to d , and variances of log odds ratios were converted to variances of d , assuming a continuous logistic distribution underlies each discrete trait (Hasselblad & Hedges 1995). Finally, we estimated Hedge's g and its variance by applying 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, stressor effects and sampling errors were not independent, as they shared 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). We included these variance-covariance matrices in our statistical analyses (see below). For a few experiments (n = 8) where large covariances between effects and small sample sizes resulted in variance-covariance matrices with negative eigenvalues (i.e., not positive definite), we adjusted 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 results with estimated covariances and show results under the RVE in Supporting Material.

Moderators

Our first analysis aimed to determine whether pathogen exposure in selected studies led to reduced host fitness without environmental stressors. For this analysis, we used the response trait category (fecundity or survivorship) as the only moderator and included only data from hosts in control (i.e., no environmental stress) conditions. We then focused on effects of environmental stressors on host-pathogen dynamics and examined three factors that could moderate the magnitude of these effects. For Q1, we considered infection status (infected and uninfected), stressor type, and response trait (fecundity and survivorship) as moderators. 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 (e.g., temperature, humidity, salinity, dissolved oxygen, and habitat structural complexity), 2) chemical pollution by toxins or synthetic compounds typically derived from pesticides or herbicides, and 3) resource limitation (restricted access to food or specific nutrients, like nitrogen and phosphorus). For response traits, fecundity was typically recorded as 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. We aimed to contrast 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 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, mean number of cercaria for helminths, and spore counts for fungi. To compare relative sensitivity of fitness and infectivity, and because prevalence and infection intensity represent 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.

We complemented these main models for Q2 with two additional moderators in separate analyses. We investigated whether transmission environment (terrestrial or aquatic) or transmission mode (direct or indirect) modulates effects of environmental stressors on infectivity and host fitness responses. For hosts that occupy different environments across life stages, we categorized transmission environment based on life stage of hosts exposed or infected in each study, which was typically the most susceptible life stage to the target pathogen. We classified pathogen transmission as 'indirect' if it met one of three conditions: 1) pathogen required an ecologically distinct intermediate host to complete its life cycle, 2) pathogen was transmitted between ecologically similar hosts via vectors, or 3) pathogen could survive independently of host during free-living stage. Otherwise, pathogens were considered as having 'direct' transmission between ecologically similar hosts.

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 non-independence of effects and sampling errors measured in the experiment. Models also included observation-level random intercepts, so residual variation within studies could be estimated. Full and reduced models (including 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 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 effects of moderators in final models. Meta-analysis results were plotted using the R package *orchaRd* (Nakagawa *et al.*2021). We tested 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 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 observation-level variances to estimate I^2. While this is not ideal, we note that meta-analytic effects of moderators accounting for sampling-error covariances are robust to these simpler models after adjustment with 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 selected models as random effect models and computed residual effect sizes conditional on experiment, observation, and factor level, for factors included as moderators in the main analyses. These conditional residuals have the advantage of taking some within-experiment non-independence into account, but they still make unlikely assumptions about sampling variances (Nakagawa *et al.* 2022).

We, therefore, complemented 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, SE of effect sizes is included as the only moderator in a meta-regression with the same random effect structure as 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 891 effects (Fig. 1). While most studies reported results from a single experiment, 21 studies included two to four experiments, resulting in a total of 122 experiments. Host taxa included arthropods (n = 20 species, classes Brachiopoda, Copepoda, Insecta, and Malacostraca),

molluscs (n = 13 species, classes Bivalvia and Gastropoda), fish (n = 13 species), amphibians (n = 21 species), and several vertebrates species (two bird, one reptile, and one mammal) (Fig. S1a). Parasite taxa comprised viruses (n = 37), bacteria (n = 14), fungi (n = 6), parasitic animals (n = 13, helminths and myxozoan), and protozoans (n = 8) (Fig. S1b).

Q1: Fitness effects of stressors on infected and uninfected hosts

After confirming that pathogen infections in surveyed literature reduce host fitness (Fig. S2; Fig. S3; Table S1), we asked if effects of stressors on fitness are modulated by infection status (Q1). The lowest AICc model for Q1 included stressor type, response trait, and their interaction as moderators (Table S2). Our data, therefore, does not support differential effects of environmental stressors between infected and uninfected hosts (Fig. S4). The interaction between stressor type and response trait resulted primarily from a relatively strong negative effect of resource limitation on fecundity (Table S3; Fig. 2) and a relatively strong negative effect of endogenous environmental stressors on survivorship (Table S3; Fig. 2). Pollution also negatively affected survivorship (Table S3; Fig. 2), but this effect was contingent on results of low precision studies (see Evidence of publication bias). These contrasting effects of the three stressor types were qualitatively similar if the RVE was used instead of modeling sampling-error covariances (Fig. S5). Differences in effect sizes both within ($I^2 = 40.42\%$) and between ($I^2 = 53.41\%$) experiments contributed to relatively high total heterogeneity ($I^2 = 93.83\%$).

Q2: Sensitivity of host fitness and infectivity responses to stress

We contrasted fitness and infectivity effects of stressors on infected hosts. The full model, including stressor type, response trait, and their interaction, had the lowest AICc score (Table S4). In this model, the interaction arose not only due to differential sensitivity of fecundity and survivorship responses to stressor type but also because the direction of infectivity responses only aligned with fitness responses for endogenous environmental stressors (Table S5; Fig. 3). Effects of resource limitation differed 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 S5; Fig. 3). In contrast, chemical pollution impacted survivorship more than 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 S5). Finally, perturbation of the endogenous environment tended to decrease host survival and increase pathogen intensity, both of which had negative consequences for host fitness and health (Table S5; Fig. 3, all infectivity vs. fitness contrasts $p > 0.05$; however, survivorship vs. prevalence: $p = 0.057$).

We obtained a similar pattern of interaction among stressors and fitness and infectivity responses when the RVE was used to account for non-independence of sampling errors (Fig. S6). Despite these contrasting effects of moderators, heterogeneity remained high (total $I^2 = 90.26\%$), both between ($I^2 = 64.11\%$) and within ($I^2 = 25.15\%$) experiments.

Effects of stressors on host fitness and infectivity traits also depended on environment and mode of pathogen transmission. While the negative effect of resource limitation on host fecundity was consistent in both environments, resource limitation only lowered pathogen intensity for aquatic hosts (Table S6; Fig. S7). Similarly, chemical pollution reduced pathogen prevalence, and endogenous environmental stressors reduced host survivorship and increased infection intensity in aquatic but not terrestrial hosts (Table S6; Fig. S7). For host-pathogen systems with indirect transmission modes, resource limitation decreased host fecundity and pathogen intensity, and chemical pollution reduced host survival and pathogen prevalence (Table S7; Fig. S8). While effects of endogenous environmental stressors were generally consistent between transmission modes, mortality was more pronounced in hosts exposed to pathogens with direct transmission (Table S7; Fig. S8). Although our results show potential distinctions and similarities between environments and transmission modes, we note that most effects were from aquatic (495 of 686) and indirect transmission (509 of 686) systems, possibly biasing our findings towards these systems.

Evidence of publication bias

More negative effects of stressors in studies with lower precision suggest that 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 S8). We thus adjusted meta-analytic estimates for analyses in Q1 and Q2 by including variance as an additional moderator in both models.

Some results in Q1 differed qualitatively after adjusting for small study effects. Specifically, effects of endogenous environmental stressors and pollution became non-significant when variance was included as a moderator (Table S9; Fig. S9). 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 few studies (n = 8).

In Q2, our qualitative results remained essentially unchanged after adjusting for publication bias. Overall, effects of endogenous environmental stressors reduced host survival and increased both infectivity traits (Table S10; Fig. S10). 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 S10). Finally, the negative impact of chemical pollution on host survival and prevalence in our primary analysis (Table S5; Fig. 3) became indistinguishable from zero in the adjusted model (Table S10; Fig. S10). 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 effects of stress on infected host fitness and infectivity, responses varied depending on stressor type. 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 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 epidemiological dynamics of each model across a gradient of either resource availability or environmental stress, then plotted 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 (Fig. S11). Therefore, in all scenarios of sensitivity of pathogen transmissibility to resources (smaller values of the half-saturation transmission constant (h_t) increase sensitivity of transmission rate (β) to resources), the model reaches the same prevalence equilibrium. However, although population density also stabilizes,

impacts on host density are different for each scenario: populations more sensitive to resources available will reach smaller population sizes compared to less sensitive populations (Fig. 5C)

The SI-Environmental stress gradient models revealed that population density decreases regardless of 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 stress increases and persists, populations will decline after pathogen extirpation (Fig. 5D). Importantly, our models suggest that high pathogen prevalence and/or stressors can result in host population extinction.

Our models illustrate that 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 in relation to 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 this differential response could be due to 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 invest resources in immune defense 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 investment in other physiological processes (Hite *et al.* 2020). For example, Cumnock *et al.* (2018) showed that malaria-infected mice reduced their food intake and switched from burning sugar (glycolysis) to fats (ketosis), which influenced host tolerance to infections. Alternatively, resource limitation could negatively affect pathogens, decreasing their capacity to reproduce within hosts. Lastly, resource-limited hosts are often smaller and may carry fewer pathogens, reducing pathogen intensity. 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 stressed hosts 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). When stressed, hosts may not resist infections (increasing pathogen proliferation) and/or compensate for damage done by the pathogen (tolerating infection), as seen when higher temperatures increase coral (*Gorgonia ventalina*) susceptibility to fungus (*Aspergillus sydowii*), while also

increasing fungal growth and virulence (Ward*et al.* 2007).

Finally, we found hosts exposed to pollutants had higher mortality but lower pathogen prevalence. However, we note that these results must be interpreted cautiously, given that the experimental studies included in our meta-analysis intentionally used sub-lethal toxin doses. 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, mortality increased in infected hosts as zinc concentration increased, but parasite burden peaked at intermediate zinc concentrations in a fish-parasite system (Gheorgiu *et al.* 2006). 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 impact population dynamics. The worldwide amphibian decline constitutes an important example. Although mass amphibian mortalities have been linked to chytrid fungus infections (Lötters *et al.* 2009), the pathogen alone is not sufficient to cause of ongoing declines (Alford *et al.* 2007; Rollins-Smith *et al.* 2011; Scheele *et al.* 2019). Global warming, another culprit of population declines, degrades amphibian condition (Reading 2007), increasing susceptibility to the fungus (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 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). It is important to note that other strategies to monitor and manage wildlife diseases exist, like targeted surveillance on single species that dominate transmission (Streicker *et al.* 2013; Charlier *et al.* 2022).

Effects of multiple stressors (e.g., environmental stressors plus infection) can perpetuate cycles, where hosts in poor condition may not respond adequately to infection (e.g., reduced infection resistance or tolerance), further reducing their condition and increasing susceptibility to stressors and additional infections (Beldomenico & Begon 2016). As most known pathogens are multi-host (Woolhouse *et al.* 2001), such cycles could affect population and community-level dynamics (Beldomenico & Begon 2016). For example, 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 other species. White-nose syndrome, an emerging fungal disease in bats, constitutes another notable example. While the disease has severely decimated some bat species populations, other sympatric and closely related species have been largely unaffected while sustaining transmission (Langwig *et al.* 2012, 2016; Cheng *et al.*2021).

Although most of the taxa examined (arthropods, molluscs, amphibians, and fish) are not commonly associated with zoonotic events, insights are gained by identifying generalities across taxa and comparing them with other systems. For instance, we found that pathogen intensity increased in hosts exposed to environmental stressors, suggesting negative implications for public health. Under stressful conditions, individuals could become superspreaders, amplifying pathogen transmission potential and disease risk (Lloyd-Smith *et al.* 2005; Gervasi *et al.*2015; Faust *et al.* 2017). Consequently, they could increase intra- and inter-species transmission and pose a risk for spillover to humans and domesticated animals (Plowright *et al.* 2017; Faust*et al.* 2018). For example, nutritional stress has been identified a primary risk factors for Hendra virus infection in flying foxes (*Pteropus* sp.), leading to 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 analyses included only 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 stressor effects in host-pathogen interactions, is difficult to translate to the natural world, where populations are likely exposed to multiple pathogens and a combination of stressors. When considering co-infections, for instance, stressors may 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 (where 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 pathogens 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 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 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 toward 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 is crucial to understanding their roles in infectious disease dynamics. 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 pathogen 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 predicted patterns.

Finally, our study 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 rodent study 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 stressor effects 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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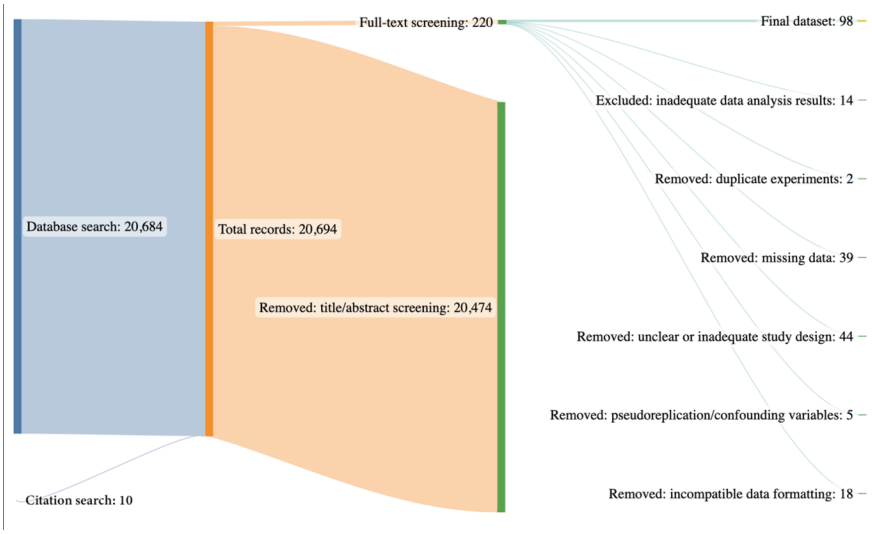

Figure 1. PRISMA diagram documenting our study screening for inclusion and exclusion for the meta-analysis. Each stage of the data collection process is highlighted with different colored pipes (blue: literature search; orange: title/abstract screening; green: full-text screening).

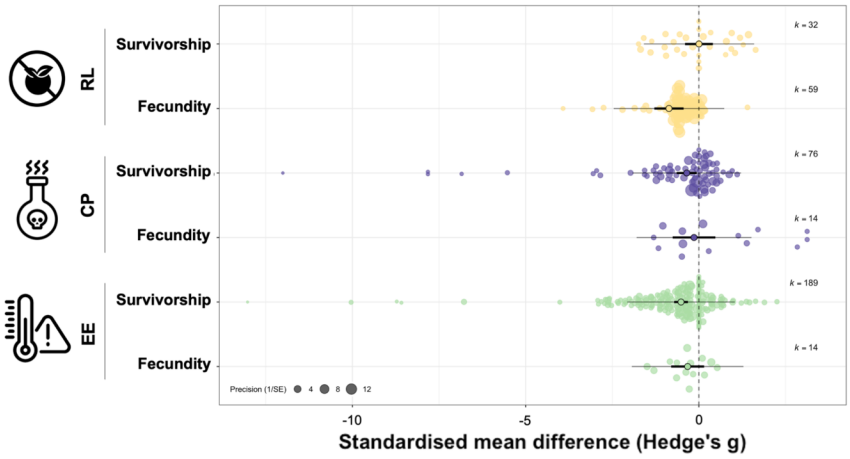

Figure 2. Orchard plot for the best multi-level meta-analytic (MLMA) model of the effects of environmental stressors on host fitness traits. The model includes two factorial moderators: stressor type, coded as "endogenous environment" (EE), "chemical pollution" (CP), and "resource limitation" (RL), and 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.

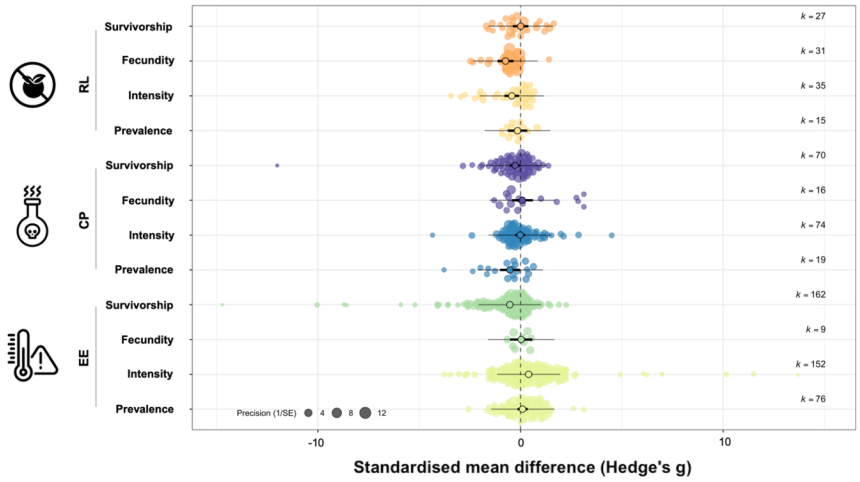

Figure 3. Orchard plot for the best multi-level meta-analytic (MLMA) model of the effects of environmental stressors on host fitness traits and infectivity. The model includes two factorial moderators: stressor type, coded as "endogenous environment" (EE), "chemical pollution" (CP), and "resource limitation" (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.

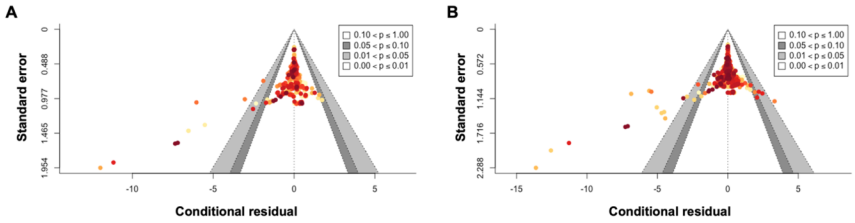

Figure 4 . Funnel plots showing the relation between precision (SE) and conditional residuals of the effects of environmental stressors on A) fitness and B) fitness and infectivity responses in animal hosts. Dark and light grey areas show bounds of 90% and 95% CIs for conditional residuals given the 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

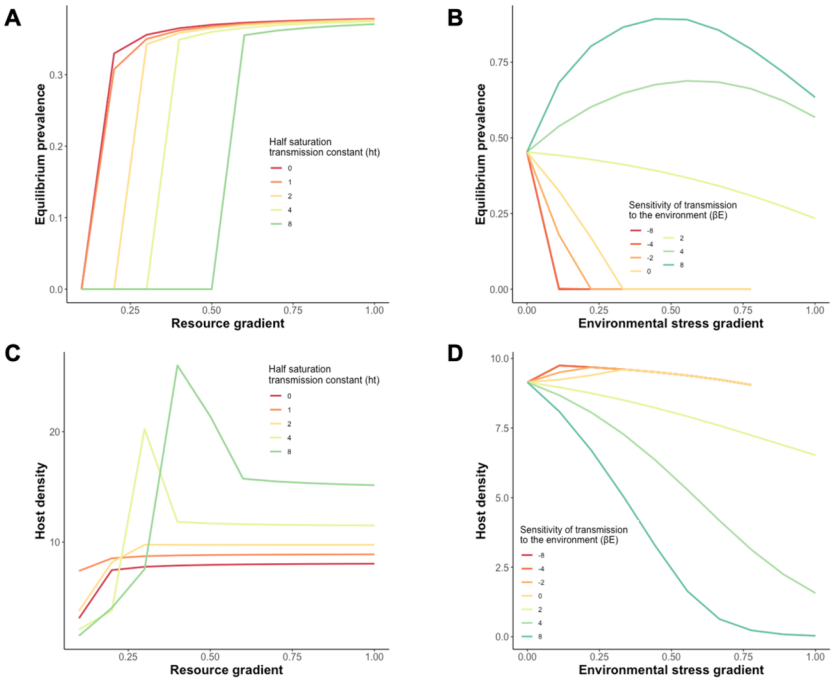

Figure 5. Contrasting outcomes for equilibrium prevalence (A and B) and host density (C and D) from hypothetical epidemiological models that illustrate dynamics that rise when fitness traits (survival and fecundity) and infectivity (transmission rate) vary with stressors, as demonstrated by our meta-analysis 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.