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CellPress REVIEWS

Review

Starving the Enemy? Feeding Behavior Shapes Host-Parasite Interactions

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The loss of appetite that typically accompanies infection or mere exposure to parasites is traditionally considered a negative byproduct of infection, benefitting neither the host nor the parasite. Numerous medical and veterinary practices directly or indirectly subvert this 'illness-mediated anorexia'. However, the ecological factors that influence it, its effects on disease outcomes, and why it evolved remain poorly resolved. We explore how hosts use anorexia to defend against infection and how parasites manipulate anorexia to enhance transmission. Then, we use a coevolutionary model to illustrate how shifts in the magnitude of anorexia (e.g., via drugs) affect disease dynamics and virulence evolution. Anorexia could be exploited to improve disease management; we propose an interdisciplinary approach to minimize unintended consequences.

Highlights

Host defense mechanisms fundamentally shape disease dynamics and virulence evolution.

Feeding behaviors may play a critical, but overlooked, role in host defense and evolutionary epidemiology.

Specifically, hosts typically reduce their feed intake in response to both realized and potential infections, despite the fact that defense mechanisms are energetically costly. The decline in feeding ('illness-mediated anorexia') shifts within-host energetics, metabolism, physiology, and immune functions in ways that alter the selective pressures facing parasites.

Consequentially, illness-mediated anorexia may drive the evolution of higher or lower virulence, depending on its interactive effects on immunological and parasitological processes.

Examining illness-mediated anorexia through the lens of evolutionary epidemiology carries important implications for disease management, especially for livestock and fish.

Why Appetite during Illness Matters

When we feel sick our appetite often declines and we may crave specific foods. These appetite changes are well known as the first sign of preclinical illness in hosts ranging from fruit flies to humans and infectious agents ranging from viruses to helminths [1–4]. While the occurrence of this behavior is well documented, the environmental factors that influence it, the reasons it evolved, and its effects on disease outcomes remain poorly resolved [5–8]. Nonetheless, this so-called '**illness-mediated anorexia**' (see Glossary) is typically considered a negative byproduct of infection, benefitting neither the host nor the parasite, and is largely taken for granted. Many common medical and veterinary interventions (e.g., use of antimicrobials, nonsteroidal anti-inflammatory drugs like ibuprofen) directly or indirectly inhibit the magnitude or duration of anorexia without considering the potential epidemiological consequences [9–12] (Table S2 in the supplemental information online).

We suggest that these common protocols, and indeed evolutionary ecology in general, overlook three crucial points that warrant serious consideration. First, anorexia can alter host defense by affecting both **resistance**, which is the ability to control parasite growth and reproduction, and **tolerance**, which helps the host reduce infection-induced pathology [5,6,13,14]. Second, mounting evidence indicates that parasites (e.g., the protozoan *Leishmania*, parasitoids, *Salmonella*) can directly alter the feeding behaviors of their hosts to increase transmission to new hosts [5,15]. Third, given these effects, anorexia-mediated factors may carry important, but overlooked, implications for evolutionary epidemiology because they change the selective pressures facing parasites; just as parasites are known to evolve in response to vaccine and antimicrobial interventions, could also evolve in response to anorexia-mediated changes within the host. Thus, the numerous medical and veterinary protocols that directly or indirectly subvert anorexia could have unintended consequences for public health concerns such as **virulence** evolution [16–18]. An important research objective, therefore, is to better understand how anorexia affects the processes that govern parasite evolution.

Understanding the evolutionary (and possibly coevolutionary) drivers and consequences of anorexia could improve efforts to harness host nutrition and feeding behaviors to improve the efficacy of drugs while also reducing their negative side effects [19–22]. To make such approaches more resistant to parasite evolution, a better understanding of how anorexia affects parasite traits is essential [23–26]. Note that we use the term 'parasite' to refer collectively to all infectious agents, including single-celled bacteria, multicellular eukaryotes, and viruses.

Our goal here is to advance this endeavor by considering how anorexia affects disease dynamics through multiple resistance mechanisms, tolerance, and parasite coercion (i.e., where the parasite

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modulates the host's feeding behavior to increase transmission). We discuss each of these scenarios and use evolutionary theory [17,24,27] to examine how changes in anorexia (e.g., via medical interventions) might alter the size and severity of epidemics. This theory-guided perspective underscores that, beyond immune cells, defense against parasites involves an integrated and adaptively plastic arsenal of beneficial microbes and behavioral, physiological, and metabolic changes [28–32]. We present an evolutionary epidemiologist's introduction to illness-mediated anorexia in Boxes 1 and 2. We close by identifying key gaps for future empirical studies and discuss how this information could be applied to improve host health and disease management.

Linking Anorexia to Host Resistance and Tolerance

Illness-mediated anorexia functions, at least in part, as a first line of defense and results in substantial declines in food intake (in the range 2–100%) that may occur within seconds of mere exposure to live or even sterilized/deactivated parasites or during later phases of infection [2,4,33]. In cases of early and rapid response, anorexia appears to be a generalized defense and does not require an active infection *per se* [2,6,28,32,33]. Additionally, the magnitude of anorexia appears finely tuned to the severity of the threat; anorexia becomes stronger with higher levels of parasite exposure or parasitemia, as seen, for example, in fish [34–36], sheep [20,37], frogs [38], rabbits [39], and zooplankton [40,41]. More susceptible host genotypes [42] and stages [37,40,42–44] also appear to exhibit stronger anorexia than their less susceptible counterparts. Additionally, individual-level differences in the magnitude and duration of anorexia may help to explain why some individuals either succumb to infection and die or clear the infection and recover [45].

From an evolutionary perspective, it makes sense that anorexia should be both sensitive and phenotypically plastic. Defense mechanisms are costly; they can cause self-harm (**immunopathology**) and divert resources that would otherwise support growth and reproduction [31,46,47]. Hence, hosts must balance the relative costs and benefits of what and how much to eat in light of their current contexts. Still, not eating seems to contravene both intuitive wisdom and classical models: why stop eating during such an energetically demanding time? We propose that considering host defense as a varied and phenotypically plastic arsenal has the potential to reveal the circumstances in which illness-mediated anorexia reflects host defense or parasite manipulation. For instance, for the diverse array of hosts that become infected through contaminated food (e.g., dung beetles, sheep, cows, horses, reindeer [43,48,49]), rapidly detecting and responding to such threats could reduce the probability of infection by limiting further contact with infectious agents. Thus, anorexia could function as an avoidance or 'anti-infection' resistance mechanism [17,18,50]. Alternatively, anorexia may counterintuitively enhance immune functions by reducing costs associated with resource acquisition, detoxification, or digestion, all of which can interfere or trade off against immune function [51–53]. Thus, anorexia could function as an 'antigrowth' mechanism by promoting an effective immune response [17,18,50].

Recent studies suggest that anorexia is more nuanced than previously appreciated and plays a pivotal role in **self-medication**, whereby hosts modulate their total energy/calorie intake as well as specific ratios of macronutrients [54–56]. For example, in crickets, the protein apolipoprotein III is involved in both lipid transport and immune function such that a high-fat diet creates a trade-off between the immune system and digestion, consequently reducing host resistance to bacterial infection [51]. When offered a choice between high- versus low-fat diets, infected crickets not only ate less but also preferred foods with lower fat content. Similarly, virus-challenged caterpillars reduce their overall food intake and increase the protein-to-carbohydrate ratio of their diet by markedly reducing their carbohydrate intake rather than increasing protein intake as previously assumed [56]. Hence, depending on the specific nutritional resources that are available, anorexia may help hosts bias the direction of physiological trade-offs to **optimize** immune functions.

Beyond shifts in macronutrient intake, anorexia is also associated with increased metabolic rates and altered metabolism of carbohydrates, lipids, and proteins [13,57,58]. For example, Cumnock *et al.* [13] illustrated that malaria-infected mice become strongly anorexic and switch their metabolism from

Glossary

Coevolutionarily stable strategy (CoESS): the set of quantitative trait values expressed by both the host and the parasite that cannot be invaded by nearby trait values for either the host or parasite. The strategies we examine here are anorexia, exploitation, and virulence.

Evolutionarily stable strategy (ESS): the value of a quantitative trait (of the host or parasite) such that a population expressing this trait cannot be invaded by populations expressing a nearby trait value.

Exploitation: the rate at which parasites steal resources from the host for their own growth and development, which, in turn, can affect virulence with concomitant changes in the shedding of infectious propagules into the environment.

Fitness: refers to the reproductive success of an individual (host or parasite), which involves both reproduction and survival and is measured in terms of genetic representation in the next generation.

Illness-mediated anorexia: a usually temporary but substantial reduction in voluntary food intake that accompanies exposure to or infection by infectious agents (parasites and pathogens) and other antigenic challenges [e.g., lipopolysaccharide (LPS) or poly(I:C), which mimic generalized bacterial and viral infections, respectively]; can occur in uninfected and infected individuals alike; also known as parasite-induced anorexia, foraging-rate depression, often studied using calorie restriction. Illness-mediated anorexia is the most frequently used term for this condition, so we use it here for consistency's sake, although there are likely to be many other, more appropriate terms. Note, it should not be confused with anorexia cachexia (a life-threatening condition associated with several pathologies and characterized by massive loss of body mass, anorexia, general inflammation, and pronounced muscle wasting) or anorexia nervosa (an emotional dysregulation characterized by an obsessive desire to lose weight by refusing to eat).

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glycolysis (primarily burning sugar) to ketosis (primarily burning fats). Is this a common pattern found across other host–parasite systems? Do such anorexia-mediated shifts in host physiology and bioenergetics affect the size and severity of epidemics? One particularly powerful way to address these questions is to compare cases in which anorexia functions as 'antigrowth resistance' [17,18,50] with cases in which anorexia helps to reduce the **fitness** costs associated with infection-mediated pathology (i.e., 'tolerance' [59,60]).

To date, empirical studies linking anorexia to antigrowth resistance and tolerance show heterogeneous and highly system-specific results. For instance, *Drosophila melanogaster* exhibits anorexia when infected with *Salmonella typhimurium* and *Listeria monocytogenes* [6]. In *Listeria*-infected flies, diet restriction (mimicking the anorexic response) reduced host resistance by immune inhibition (specifically, melanization) allowing parasites to increase, causing more severe disease (i.e., via systemic, extracellular infections) and thus increasing host mortality. With *Salmonella* infections, however, diet restriction increased host tolerance; it had no effect on parasite clearance or parasite load, yet infected hosts lived longer. Studies with mice and the same pathogens showed the opposite patterns: both anorexia and diet restriction increased host life span during *Listeria* infections [61] but not during *Salmonella* infections [5]. Additionally, in malaria-infected mice, anorexia decreased tolerance [13].

These studies have greatly advanced our understanding of the molecular and physiological underpinnings of anorexia and join others highlighting how anorexia alters the within-host environment via shifts in microbiota [62], immunology, physiology, metabolism, and energy allocation [2,28,30,51,53]. However, scaling up these findings to the individual and population level and to a more diverse array of host–parasite systems remains crucial to understanding the epidemiological and evolutionary consequences of anorexia [2,26,63,64].

Parasite Manipulation of Host Anorexia

Further complicating our understanding of the higher-order implications of anorexia is the potential for parasites to manipulate, directly or indirectly, the feeding behaviors of their hosts (with concomitant changes to within-host conditions). Although parasites are notorious for manipulating host phenotypes to their own ends, the role of parasite-mediated manipulation of host feeding behaviors in general, and anorexia in particular, remain largely unexplored, as evidenced by classic textbook examples [65] and recent reviews [66–68]. This gap is surprising given that the manipulation of food intake may represent an efficient way for parasites to simultaneously alter several aspects of the within-host environment and, thus, transmission potential [5,8,15,69].

Salmonella-infected mice exhibit anorexia, which leads to a more systemic and severe infection (due to extraintestinal dissemination) such that hosts die quickly, shedding fewer propagules into the environment and reducing transmission to new hosts [5]. However, some strains of the parasite can inhibit anorexia (via the gut–brain axis), leading to less severe infections, prolonged host survival, increased within-host parasite load, higher rates of shedding, and, subsequently, increased transmission to new hosts. In other words, in this model system, anorexia appears to function in antitransmission resistance and creates a trade-off between virulence and transmission.

Additionally, detailed molecular work with parasitoid wasps (*Cotesia congregata*) illustrates that they manipulate host neuromodulators, inducing their caterpillar hosts to stop feeding altogether [32,70–72]. This change is finely tuned to the timing of parasitoid emergence and presumably prevents the host from accidentally consuming the larvae, which, in turn, promotes parasitoid emergence, likely improving future transmission events.

Parasite-mediated changes to vector feeding behavior may also promote transmission [73–75]. For instance, an impressive study by Rogers and Bates [15] illustrated that the protozoan parasites *Leishmania mexicana* and *Leishmania infantum* alter the feeding behavior of their vectors (sand flies) in several ways, all of which are finely tuned to transmission stages. In a series of elegant experiments, the authors showed that this parasite-mediated shift in feeding may increase transmission to

Immunopathology: harm, hypersensitivity, or disease arising from activity of the immune system.
Optimize: used here to refer to the trait value that maximizes a fitness expression, given a set of constraints or life-history trade-offs.
Resistance: the ability to control parasite levels; can occur by preventing the establishment of parasite infection or reducing the infective dose (known as 'anti-infection resistance' or avoidance) or reducing the parasite growth or burden within infected hosts (known as 'antigrowth resistance' or clearance).
Self-medication: use of a third species or compounds by hosts to reduce the likelihood of specific compounds infection (can occur in uninfected and infected individuals alike) or to fight or inhibit parasite growth once infected (occurs in infected individuals).
Sickness behaviors: stereotypical behavioral changes that accompany different phases of exposure to or infection by parasites and pathogens – anorexia, fever, lethargy, somnolence, and decreased libido.
Tolerance: a reduction in infection-induced pathology (e.g., fecundity loss, mortality) that does not reduce parasite infection or growth.
Virulence: parasite-induced reduction in host fitness; often equated with the disease-induced mortality rate and therefore involves both direct harm from the parasite and associated immunopathology.

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Box 1. What Is Illness-Mediated Anorexia? A Synopsis

Illness-mediated anorexia (hereafter, 'anorexia') is a well-known component in a larger suite of so-called 'sickness behaviors', which include lethargy and fever and are part of the acute-phase response (APR) of the innate immune system [1–3] (Figure I, Key Figure). Anorexia functions, at least in part, as a first line of defense that can lead to rapid and substantial declines in food intake (range 2–100%) within seconds of mere exposure to live or even sterilized/deactivated parasites. In this regard, the decline in food intake appears to be a generalized defense and does not require an active infection *per se* [2,6,28,32,33] (Table S1).

Key Figure

An Overview of Illness-Mediated Anorexia through the Lens of Evolutionary Epidemiology

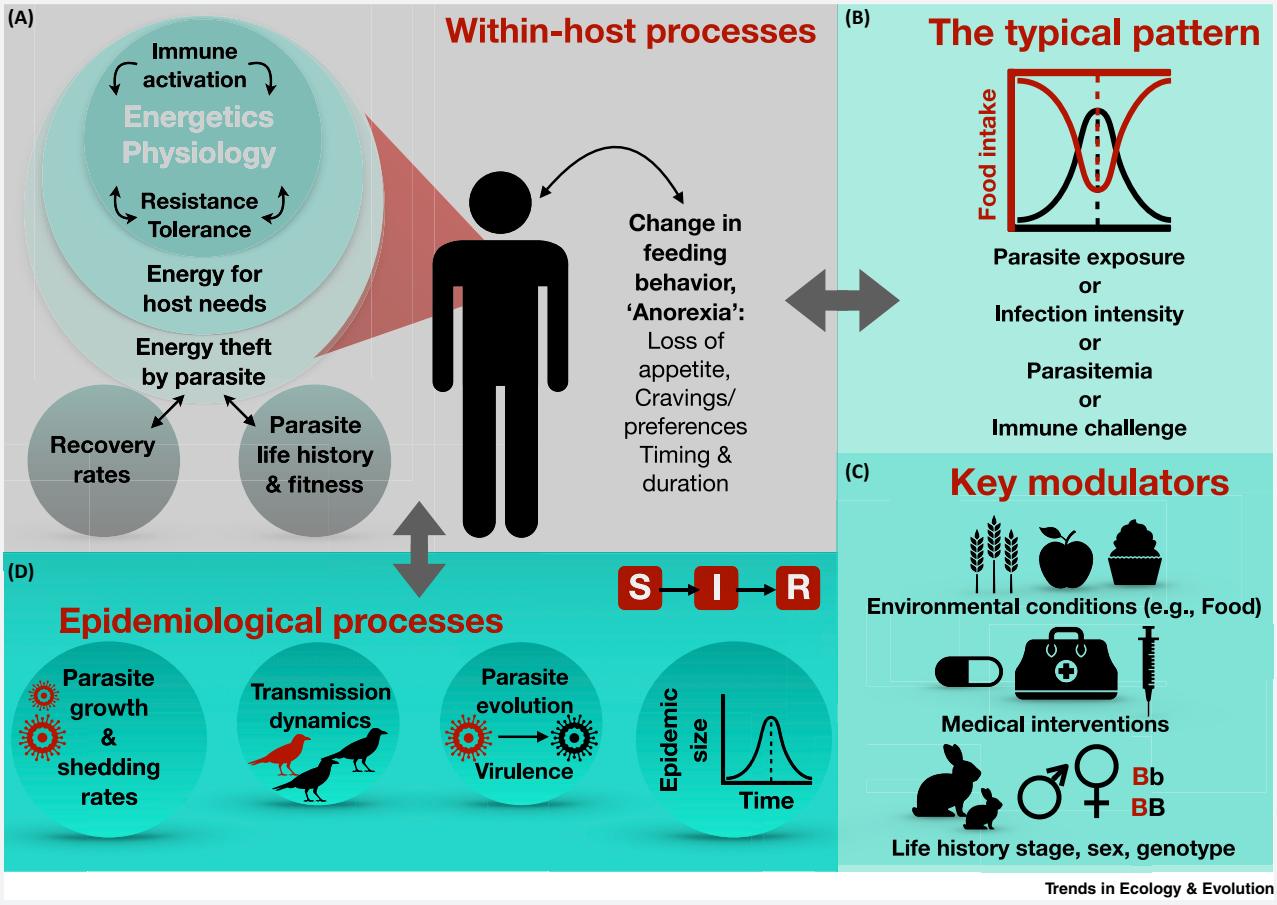

Figure 1. (**A**) As part of the acute phase response, anorexia is modulated by a complex suite of changes *within hosts*. For example, in vertebrates, anorexia is governed, in part, by cytokines (e.g., tumor necrosis factor [TNF], interleukin 1B [IL-1B], interleukin 6 [IL-6], hormones [e.g., ghrelin]). Anorexia is also linked with other downstream energetic and physiological changes, other sickness behaviors such as fever, and additional immune functions (and associated immunopathology), all of which change the energy available to support basic life history needs (e.g., growth, reproduction) and to be exploited by parasites to support their own growth and development. These changes, in turn, affect disease severity and recovery rates but also parasite life history and fitness. (**B**) A sensitive and finely-tuned first line of dense, the magnitude of anorexia (i.e., the decline in food intake) is typically dose-dependent, increasing with parasite exposure, infection intensity, parasitemia, or immune challenge. (**C**) The onset, magnitude, and duration of anorexia appears to change with environmental conditions (especially food), many common medical and veterinary practices (e.g., drugs), and host condition (e.g., breeding vs. migratory; juvenile vs. adult; male vs. female; genotype). (**D**) Anorexia-mediated changes within hosts likely alter key epidemiological processes, alter the benefits and costs of exploitation and can therefore select for more or less virulent pathogens and affect the size/severity of epidemics.

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mammalian hosts. First, infected flies consume less blood, characterizing the anorexic symptom. In this case, however, the reduced intake of blood arises not through an immune-mediated defense but through parasite manipulation. The parasite secretes a gel-like plug that, in combination with vector saliva, appears to facilitate cutaneous infections [73], blocks the vector's gut and mouthparts, and interferes with feeding. Second, presumably because of this plug, infected flies, which obtain only partial blood meals, become more persistent, nonplussed by disturbance. Hosts also choose more diverse hosts on which to feed, potentially increasing the likelihood of transmission.

In other systems (e.g., malaria, trypanosomes), similar changes in the feeding behavior of vectors could reveal general patterns and offer novel opportunities for disease mitigation [69,74–76]. For instance, the gel-like plug secreted by *Leishmania* shares striking similarities with the biofilm of *Yersinia pestis* (plague) that also alters flea biting behavior, increasing transmission (see [15,73] for detailed information). These exceptional studies represent the rare few that link anorexia to both host and parasite traits. However, they are often conducted in laboratory settings that omit the risk associated with feeding behavior, which is especially important in vector survival and population dynamics. Hence, the relative importance of illness-mediated anorexia in facilitating transmission via vectors represents a rich avenue for future investigations.

On the Need for a More Integrated Perspective of Illness-Mediated Anorexia

The current empirical gaps outlined here impede efforts to examine why anorexia evolved and appears to be highly conserved in hosts ranging from insects to sheep to humans (Box 2, Table 1, and Table S1). Does anorexia generally help or hinder host recovery? Does changing anorexia select for more or less virulent parasites? Answers to these questions carry implications for both basic science and public health. Again, anorexia is typically considered a maladaptive trait or simply a byproduct of infection [4,6,11,33]. Thus, from a public health perspective, identifying the contexts in which anorexia benefits the host more than the parasite (and vice versa) could lead to more forward thinking and 'evolution-proof' programs for managing host health and disease [22,23].

Integrating Illness-Mediated Anorexia into Epidemiological Theory

To examine how anorexia affects disease dynamics through multiple resistance mechanisms, tolerance, and parasite coercion, we integrate our empirical findings into an epidemiological model [24,50,77]. Before we begin, it is helpful to review the main conceptual framework that is used to think about how 'leaky' vaccines affect the evolution of virulence [17,27]. This body of theory indicates that the strength, and even the direction, of selection depends on whether the vaccine targets parasite infection, growth, or transmission. Consider, for example, a treatment program that targets parasite growth (e.g., vaccines, antimicrobials). One reason these treatments often fail is that they are imperfect. They inhibit parasite growth but rarely completely prevent it; consequently, they can select for faster-growing parasites that cause more harm to their hosts. Hence, imperfect vaccines that suppress parasite growth can inadvertently select for more harmful (virulent) parasites [17].

Building on this previous theory, we consider how innate or medically altered changes to illness-mediated anorexia can affect parasite evolution and disease dynamics similar to imperfect vaccines. However, unlike vaccines, which are designed to target specific parasite traits (e.g., growth, transmission), anorexia can affect multiple traits of the host and the parasite simultaneously through various pathways (Boxes 1, 3, and 4 and Table 1). Thus, predicting disease outcomes necessarily requires accounting for multiple effects of anorexia.

The model cautions that, depending on how anorexia affects different aspects of resistance and tolerance, interventions that alter host anorexia could substantially reduce disease severity – or backfire (Figure 1). In some cases, these interventions could unintentionally select for more harmful parasite strains, driving larger and more virulent epidemics. These results may be particularly important for livestock and fish, which are exposed to a wide array of orally transmitted parasites

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Box 2. What Have Studies on Illness-Mediated Anorexia Taught Us?

A wealth of studies demonstrate that illness-mediated anorexia occurs in a diverse array of vertebrate and invertebrate taxa (Figure I and Table S1). For the most part, these studies have largely taken a host-centric approach, focusing on the molecular and physiological drivers of anorexia. In reviewing over 140 studies, we found that surprisingly few studies (n = 26; 19%) collected the data needed to quantify how anorexia affects host health or disease outcomes (for data and search terms, see Tables S2–S4). Additionally, many studies use different methods for exposing or infecting hosts (e.g., oral, intraperitoneal, intravitreal), which can result in drastically different immune responses and patterns of infections. These methodological differences add to the challenge of identifying generalizable patterns across systems [7].

We propose that anorexia functions as a 'master switch' that modulates downstream changes in immunological, metabolic, and physiological pathways, which jointly influence how hosts respond to and cope with infection. However, the magnitude of anorexia – and whether it limits infection in the first place ('anti-infection resistance'), limits parasite growth ('antigrowth resistance'), helps hosts endure infection-induced pathology ('tolerance'), is manipulated by parasites to increase transmission – depends on nutrient stores and ambient conditions, particularly with regard to current dietary options available to the host and the parasite.

This dependence on dietary context arises because, while costs associated with defense can be energetically costly, not all nutritional resources are created equal; some macronutrients (e.g., fat) can interfere with immune functions [86], while others divert energy from immune functions to detoxification or digestion [53] and differentially affect parasite growth and development (e.g., iron; see [33] and references therein). Thus, hosts must balance nutrient intake and allocation in ways that optimize basic maintenance costs and immune functions while minimizing parasite survival. Similarly, the parasite must balance the host's nutrient intake in ways that optimize transmission but minimize the harm caused to the host. These points seem to highlight the obvious, but this coevolutionary perspective (i.e., one that includes the parasite) remains surprisingly absent from most studies on illness-mediated anorexia.

Moving forward, it would be helpful (although admittedly challenging) if studies on anorexia endeavored to measure six intertwined parameters: (i) food intake; (ii) immune responses; (iii) parasite growth, development, load, and/or shedding; (iv) host recovery rates; (v) harm (e.g., mortality, weight loss, fitness); and (vi) transmission.

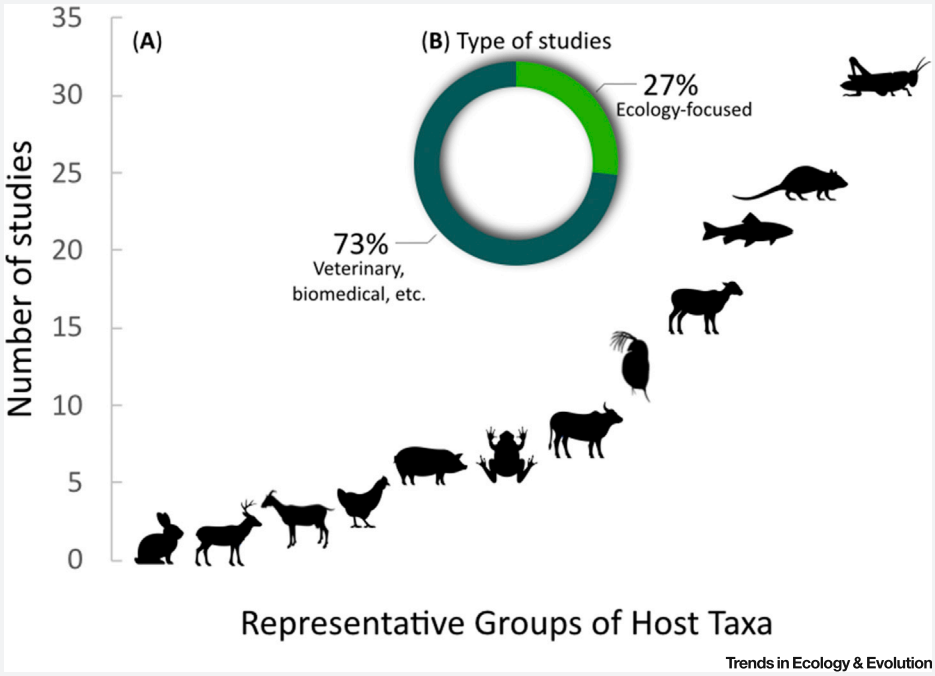

Figure I. Representative Host Taxa and Disciplines Illustrating That Illness-Mediated Anorexia Occurs in a Diverse Array of Hosts and Has Been Examined from a Range of Perspectives.

Note: The hosts here are very broadly and generally represented to provide a simple overview of the number of studies; for example, insect systems (n = 33) are denoted by a single representative, a grasshopper.

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Host	Parasite	What we know	Key open questions
 Fruit fly *Drosophila melanogaster*	*Salmonella* *Salmonella typhimurium* *Listeria* *Listeria monocytogenes* [6]	The magnitude of anorexia was stronger with *Listeria* infection relative to *Salmonella* Diet restriction (mimicking anorexia) increased tolerance to *Salmonella* but decreased resistance to *Listeria*	What molecular pathways underpin anorexia-mediated differences in immunity? How would resource type alter these outcomes?
 Green frog *Lithobates clamitans*	Chytrid (*Bd*) *Batrachochytrium dendrobatidis* [38]	The magnitude of anorexia increased with increasing *Bd*-infection intensity (i.e., dose-dependent)	How does anorexia affect immune–*Bd* interactions? How does anorexia differ across species or genotypes that differ in susceptibility to *Bd*?
 Mouse *Mus musculus*	*Salmonella* *S. typhimurium* [5]	*Salmonella* inhibited anorexia (via the vagus nerve), which then reduced disease severity, increasing host survival and transmission (at least via the oral–fecal route)	How would parasite-mediated inhibition of anorexia affect other routes of transmission (trophic, airborne)?
 Water bat *Daphnia dentifera*	Yeast *Metschnikowia bicuspidata* [40]	Anorexia occurred within hours of mere exposure to fungal spores and the magnitude of anorexia was dose dependent Anorexia varied substantially across host sex, stage, and genotype	How does anorexia affect host immune functions, resistance, and tolerance? Are host stages and genotypes with the strongest/weakest anorexia more or less resistant or tolerant? Does anorexia affect host population dynamics?
 Hawaiian honeycreeper *Hemignathus virens*	Avian malaria *Plasmodium relictum* [45]	Anorexia peaked during maximal parasitemia and appeared to limit parasite growth within hosts, increasing host recovery and survival High individual-level variation was noted in the onset and duration of anorexia	What physiological mechanisms underpin the variation in anorexia? Do individuals with stronger anorexia differ in immune profile? Could food supplementation improve host survival?
 Sheep *Ovis aries*	Nematoda *Teladorsagia circumcincta* [20,37]	Animals from genetic lines selected for rapid growth exhibited stronger and longer anorexia relative to slower-growing lines Protein supplementation did not affect anorexia but did limit parasite levels	Does anorexia help or hinder recovery of individuals? Is genetic variation in anorexia a byproduct of selection on other traits, a plastic response, or a result of genetic variation *per se*?

Table 1. A Selection of Empirical Studies Illustrating Illness-Mediated Anorexia and Highlighting Our Current Depth of Knowledge and Key Open Questions

and live in dense populations where rapid biomass production (and therefore food intake) remains paramount.

Anorexia Reduces Infection (i.e., Anti-infection Resistance)

When anorexia blocks hosts from becoming infected in the first place, either it can either have no effect on the prevalence of infection if parasite **exploitation** does not evolve (Figure 1A, unbroken line) or it can decrease prevalence if the parasite evolves (Figure 1A, broken line). This difference occurs because anorexia has no direct effect on prevalence but can indirectly affect prevalence by affecting the **evolutionarily stable strategy (ESS)** for parasite exploitation. In particular, overfeeding hosts will drive an evolutionary increase in exploitation and, hence, virulence (Figure 1B); this higher mortality

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reduces infection prevalence as infected hosts constitute a smaller proportion of the host population (see the supplemental information online for additional details). From an applied perspective, these results suggest that if interventions (e.g., drugs) or ecological factors (e.g., nutritional resources) subvert anorexia [i.e., increase food intake to levels higher than the coevolutionarily stable (CoES) α], they could inadvertently select for more harmful parasites, while at the same time lowering infection prevalence at the population level.

Anorexia Limits Parasite Growth (i.e., Antigrowth Resistance)

When anorexia suppresses parasite growth within hosts, it can reduce infection prevalence regardless of whether we account for parasite evolution (Figure 1C). However, strong anorexia can also lead to higher virulence (Figure 1D). Classical predictions suggest that antigrowth mechanisms select for fast-growing, more virulent parasites [17]. Here, anorexia reduces overall infection prevalence because although individual infections are severe, recovery rates are high, reducing the duration of infection and subsequently lowering total shedding and transmission. Additionally, anorexia decreases birth rates, reducing population density and slowing transmission even more.

As in the first case, anorexia has contrasting outcomes at the individual versus population level, although the pattern is reversed. Here, anorexia leads to more severe infections at the individual level but smaller epidemics overall. Hence, subverting anorexia (i.e., stimulating food intake to levels higher than the CoES α) could help to reduce the severity of infections at the individual level but drive larger epidemics.

Anorexia Limits Parasite Growth (i.e., Antigrowth Resistance) but with Immunopathology

If anorexia limits parasite growth but also carries costs associated with immunopathology, it will decrease infection prevalence because it increases host mortality (Figure 1E). Anorexia also drives the evolution of increased exploitation (Figure 1F). This is unsurprising, as previous theory has shown that any factor that shortens the duration of infection, including immunopathology, will tend to increase selection for more virulent parasites [17,78–80]. However, subverting anorexia also drives an increase in parasite exploitation, a worst-case scenario for disease management at both the individual and the population level. Recall that intuitive wisdom and many common medical treatments subvert the anorexic response, assuming that it is a byproduct of infection or immunopathology. Our

Box 3. A Brief Overview of Theoretical Approaches for Integrating Illness-Mediated Anorexia into a Classical Epidemiological Model

As in models of imperfect vaccines, we can study how parasites might respond evolutionarily to anorexia by considering how changes in anorexia affect the parasite's exploitation strategy, ϵ. Higher ϵ implies higher virulence. We start with a model of susceptible (S) and infected (I) hosts and free-living parasites (Z), where the magnitude of anorexia is given by the parameter α (lower α implies lower ingestion and thus stronger anorexia).

$$\dot{S} = b_S(\alpha)S + b_I(\alpha)I - \beta(\alpha)SZ - \mu S + \gamma(\alpha)I, \quad [\text{I}]$$

$$\dot{I} = \beta(\alpha)SZ - [\mu + \nu(\alpha,\epsilon) + \gamma(\alpha)]I, \text{ and} \quad [\text{II}]$$

$$\dot{Z} = \lambda(\alpha,\epsilon)I - \beta(\alpha)SZ - \delta Z. \quad [\text{III}]$$

In this model, the magnitude of anorexia can affect the rate of acquisition of a new infection (because we focus here on parasites that are transmitted orally), $\beta(\alpha)$; the recovery rate, $\gamma(\alpha)$; the mortality rate when infected [i.e., virulence, $\nu(\alpha,\epsilon)$]; and the shedding rate of the parasite, $\lambda(\alpha,\epsilon)$. These changes may carry costs for the host, captured by the effect of anorexia on the birth rate of susceptible and/or infected hosts [$b_S(\alpha)$ and $b_I(\alpha)$]: for susceptible hosts, this is the cost of avoiding infection; for infected hosts, this is the cost of resistance or tolerance. Parasite exploitation (ϵ) affects virulence [$\nu(\alpha,\epsilon)$] and shedding rate [$\lambda(\alpha,\epsilon)$] via a classic virulence–transmission trade-off [90,91]. Because our interest is primarily in the effect of anorexia, we make the standard assumption that increasing exploitation linearly increases virulence but only sublinearly increases shedding [78]. We use standard adaptive dynamics techniques to examine how α and ϵ coevolve [81,83] and to predict how altering anorexia could affect epidemiology and the evolution of virulence (Box 4).

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Box 4. A Brief Overview of Theoretical Approaches for Studying How Anorexia Affects Host and Parasite Fitness

Following evolutionary epidemiology theory, we assume that evolution will maximize the fitness of the host (R_H) or parasite (R_P), where host fitness is given by

$$R_H = \frac{b_S(\alpha)}{\beta(\alpha)Z+\mu} + \frac{\beta(\alpha)Z}{\beta(\alpha)Z+\mu}\left(\frac{b_I(\alpha)}{\mu+\nu(\alpha,\epsilon)+\gamma(\alpha)} + \frac{\gamma(\alpha)}{\mu+\nu(\alpha,\epsilon)+\gamma(\alpha)}R_H\right) \quad [I]$$

and parasite fitness by

$$R_P = \frac{\beta(\alpha)S}{\beta(\alpha)S+\delta}\left(\frac{\lambda(\alpha,\epsilon)}{\mu+\nu(\alpha,\epsilon)+\gamma(\alpha)}\right) \quad [II]$$

We discuss the biological intuition for these expressions, but see [16,92] for derivations. For R_H, consider the fate of a newborn susceptible host. On average, it will remain susceptible for $1/(\beta Z + \mu)$ time steps, reproducing at a rate b_S. The probability that it becomes infected is $\beta Z/(\beta Z + \mu)$. On average, an infected host will remain infected for $1/(\mu + \nu + \gamma)$ time steps, reproducing at a rate b_I.The probability that it recovers is $\gamma/(\mu + \nu + \gamma)$. A host that recovers returns to the susceptible class and can move through all of these transitions again. This leads to a recursive expression for fitness, with R_H occurring on both sides of the equality. For R_P, consider the fate of a free-living parasite. The probability that it successfully infects a host is $\beta S/(\beta S + \delta)$. The host will remain infected for $1/(\mu + \nu + \gamma)$ time steps and new free-living parasites will be shed from the host at the rate λ. Combined with the epidemiological model, these expressions allow us to examine how treatments that affect anorexia alter both epidemiological and evolutionary dynamics.

To do so, we identify the **coevolutionarily stable strategies (CoESSs)** for anorexia, α, and parasite exploitation, ϵ [16]. Next, we ask how shifting anorexia away from this CoESS (increasing or decreasing α) affects the size of epidemics (infection prevalence), assuming the parasite does not evolve. We then allow parasites to evolve to these within-host conditions by finding the exploitation strategy that maximizes parasite fitness at the new value of host food intake α. We compare the results for infection prevalence with and without parasite evolution to underscore the importance of including parasite traits in studies of illness-mediated anorexia.

These predictions, of course, will depend on which epidemiological processes are affected by anorexia and in particular by the functions relating the magnitude of anorexia to its costs and benefits (i.e., the shapes of the fitness trade-offs, a crucial area for future empirical studies). Here, we examine several illustrative cases to highlight the pertinent parameters and functional responses needed to test these predictions empirically.

results suggest that, even if anorexia does indeed carry immunopathological costs, stimulating host appetite or overeating when ill will backfire, both driving the evolution of more harmful parasites and increasing the overall infection prevalence.

Anorexia Limits Parasite-Induced Pathology (i.e., Tolerance)

As a tolerance mechanism, anorexia has relatively little effect on infection prevalence regardless of whether we account for parasite evolution (Figure 1G), but it does select for higher exploitation (Figure 1H). By increasing tolerance (here, reducing host mortality), anorexia reduces the fitness cost of exploitation because infected hosts live longer, continuing to shed infectious propagules into the environment, and fueling transmission, allowing more harmful parasites to evolve. These predictions mirror previous findings, which also suggested that tolerance mechanisms typically lead to the evolution of higher exploitation [59,81–83]. From an applied perspective, these results suggest that when anorexia increases tolerance, subverting anorexia (i.e., increasing food intake at levels higher than the CoES α) could help to reduce both the size and the severity of epidemics.

Anorexia: A Master Switch Subject to Parasite Manipulation

Finally, we examine how parasites could benefit by directly interfering with anorexia. Such cases could arise, for example, when anorexia promotes immune functions and recovery [51,53]. In this case, anorexia strongly decreases both infection prevalence (Figure 1I) and virulence (Figure 1J).

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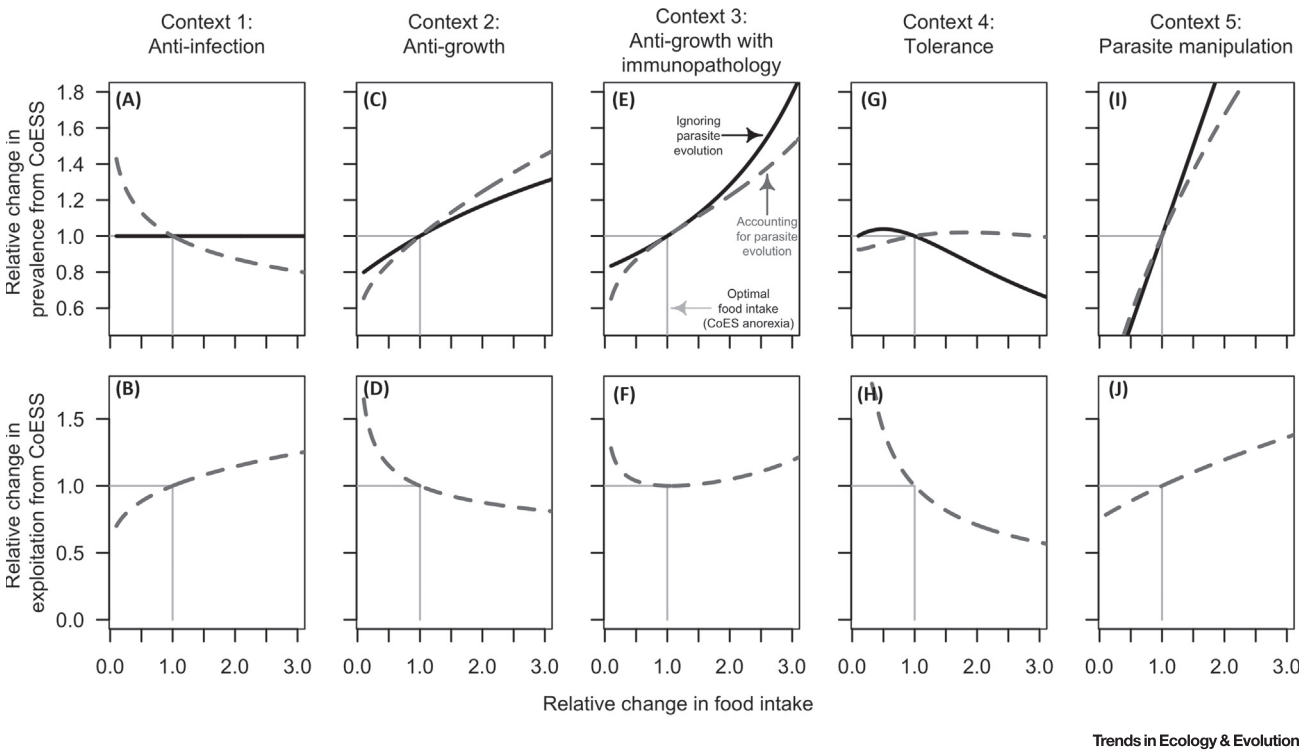

Figure 1. How Does Shifting Food Intake Away from the Coevolutionarily Stable Strategy (CoESS) α Affect the Prevalence of Infection and the Evolution of Virulence?

Our mathematical model addresses this question by examining five different contexts that capture the various ways in which anorexia can function as a resistance or tolerance strategy or be manipulated by the parasite. Top row: Theoretical predictions for how changes in anorexia affect the prevalence of infection (a population-level measurement) when either ignoring (unbroken line) or accounting for (broken line) parasite evolution. Bottom row: Theoretical predictions for how changes in anorexia affect the evolution of exploitation (parasite-induced harm to the host). In each context, changes are relative to the optimal CoESS of the host [coevolutionarily stable (CoES) α] and the parasite (CoES prevalence or exploitation). The thin gray lines denote the optimal level of food intake: CoES α (denoted on the x-axis) and the corresponding prevalence of infection; CoES prevalence (denoted on the y-axis, top row) or exploitation; CoES exploitation (denoted on the y-axis, bottom row). CoESSs are found by identifying the simultaneous vanishing of both selection gradients. Note: Shifts below CoES α reflect anorexia (or other forms of calorie restriction), whereas shifts above CoES α reflect increased appetite via parasite manipulation, drugs, or management practices that stimulate appetite.

Subverting anorexia (via parasite manipulation or medical interventions) therefore can substantially increase both the size and the severity of epidemics.

Concluding Remarks

The role of nutritional resources and calorie restriction in infectious disease is a growing topic that holds promise for improving the health of humans, wildlife, and livestock. Novel therapies are emerging that focus on prescribed calorie restriction, guided fasting, or the manipulation of certain nutrients to reduce parasite growth, burden, or transmission or to improve the host's ability to tolerate infection. Such interventions appear to have benefits at the individual level. These host-centric perspectives, however, may be short lived because they seldom consider the longer-term (evolutionary) or population-level consequences of such interventions. However, as our model illustrates, shifts in nutritional resources (e.g., via anorexia, management, medical, or environmental factors) may result in complex coevolutionary arms races.

In some senses, these findings are unsurprising; pathogens and parasites by definition steal resources from their hosts and therefore shifts in the host's nutritional resources should logically affect

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pathogens or parasites. However, as we stress throughout this review, studies that explicitly connect host resources to evolutionary epidemiology remain exceedingly rare. In animal science, eco-immunology, and biomedicine, scientists tend to study links between resources and infectious disease or between resources and immune functions, but not the trifecta. This modular approach has certainly advanced the field. However, such siloing has inadvertently left the biological causes and functional consequences of **sickness behaviors** such as illness-mediated anorexia overlooked and poorly resolved (see Outstanding Questions).

Thus, a main goal of this study was to provide both a conceptual and a theoretical framework to bridge this divide. Perhaps more importantly, by integrating physiology and evolutionary epidemiology, this review helps to extend classical views of host defense from purely immunological mechanisms to a more integrated perspective that connects host behavior, energetics, physiology, and immune functions [31,51,84–86]. We hope that this framework will help to facilitate the development of broad-scale and generalizable patterns. In particular, detailed empirical studies – using the same modes of infection (Box 2) – are needed to understand critical differences in how changes in resource quality and quantity affect vertebrates versus invertebrates [87–89]. Several model systems, such as *Drosophila*, *Daphnia*, *Caenorhabditis elegans*, birds, fish, and livestock, represent ideal candidates for these empirical gaps. These data could then be used to parameterize the model developed here to examine both epidemiological and (co)evolutionary dynamics. Such data–theory integration will help to guide the development of more 'evolution-proof' interventions [22,23] – addressing, for instance, how medical interventions could harness host nutrition to optimize host health while minimizing the evolution of virulence.

Outstanding Questions

How do management practices that directly or indirectly alter the onset, duration, and magnitude of illness-mediated anorexia affect health trajectories, disease outcomes, or virulence evolution?

When and how does anorexia affect the absolute fitness of different parasite or pathogen strains?

How does anorexia change when hosts are coinfected with multiple parasite strains or species?

How does anorexia change across host genotypes or environmental contexts?

Author Contributions

J.L.H. designed the study; J.L.H. and A.C.P. collected the data and led the writing of the manuscript; J.L.H. and C.E.C. developed the model; C.E.C. analyzed the model; all authors contributed to revisions and approved the final submission.

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