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Feedbacks between nutrition and disease in honey bee health

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Declines in honey bee health have been attributed to multiple interacting environmental stressors; among the most important are forage/nutrition deficits and parasites and pathogens. Recent studies suggest poor honey bee nutrition can exacerbate the negative impacts of infectious viral and fungal diseases, and conversely, that common honey bee parasites and pathogens can adversely affect bee nutritional physiology. This sets up the potential for harmful feedbacks between poor nutrition and infectious disease that may contribute to spiraling declines in bee health. We suggest that improving bees' nutritional resilience should be a major goal in combating challenges to bee health; this approach can buffer bees from other environmental stressors such as pathogen infection.

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Introduction

Bee pollinators live in a world of increasingly disturbed habitats, where natural areas worldwide have been transformed into more and more intensive agriculture and urban landscapes [1]. At the same time, global movement of goods, including bees themselves, has increased the speed at which pests and pathogens spread [2]. While there has been substantial interest in these two sources of stress, there has been relatively little work understanding how they interact. In the real world, these stressors are co-occurring, but understanding the complex synergy between different diseases and nutritional stresses bees face is still a developing field.

The diet of bees consists of pollen and nectar collected from flowers. Together, these products provide bees with the carbohydrates, proteins, lipids, and other nutrients they need to survive [3]. In honey bees, diverse pollen diets are preferentially consumed [4] and improve lifespan [4,5]. Some flowering plant species [5], including common mass-flowering crops [6], do not provide the necessary nutrients honey bee hives need to survive and thrive [7]. Bees' access to nutritional resources has been of increasing concern as changes in landscape use has resulted in a shift in floral resource availability and diversity, with many bees paying the dietary price [8]. The land use surrounding honey bees, for example, can have a large impact on their health and physiology [9,10]. Hives surrounded by more agricultural land show higher losses [11] and reduced fat stores entering winter [12]. However, this relationship is not always straightforward. In some landscapes more agricultural production is associated with reduced stored pollen (beebread) quality [13] (UK) and honey production [14] (Kenya); [15] (France). However, other research showed that, in parts of the Midwestern USA, honey bee hives store more honey [16] in agricultural than urban areas. Although a single coherent understanding of how landscape composition affects bee health is difficult to generalize, one thing is clear — forage availability and nutritional stress have been cited as two of the top most important challenges to bee health by researchers [3] and beekeepers [17] alike.

Another critical stressor faced by honey bees is pest and pathogen pressure. Honey bees are host to a variety of pathogens, including viruses, bacteria, fungi, as well as arthropod pests. The most detrimental of these is the Varroa mite; in addition to parasitizing developing pupae and adults, they harbor and transmit several honey bee viruses [18]. This Varroa-virus complex [19,20•,21] and the viruses alone [22,23] have been identified as major drivers in hive losses. However, other pathogens also play a role in losses. *Nosema ceranae*, a widespread microsporidian fungal gut parasite, can cause a reduction in lifespan [24,25] and hive losses [26], and European and American foulbrood are contagious bacteria that attack developing larvae and pupae [27,28].

Bee nutrition affects disease susceptibility

In many organisms, the quantity or quality of diet can affect their susceptibility to pathogens [29]. How this manifests in honey bees is still not completely understood. Pollen and nectar/honey contain variable protein, lipid, and carbohydrate content and a variety of phytochemicals and micronutrients that have the potential to affect immune response. While it is still not clear what makes the 'best' pollen, evidence suggests that a diverse diet is most likely to provide bees with the necessary inputs. Higher pollen diversity has been shown to upregulate some elements of the innate immune system [30••] and reduce mortality due to *N. ceranae* [31••] and Israeli acute paralysis virus (IAPV [32]). Protein, amino acid, and micronutrient content have all been hypothesized as contributors to these effects [31••,32,33••,34••], though no definitive driver has been identified. Likely, there is interaction between all of these components, with each playing an important role in honey bee resilience. There is still much to be learned about the mechanisms by which good diet and nutrition may provide benefits to honey bees in the form of reduced pathogenicity in the face of both viral and fungal pathogens. However, the evidence to date is compelling in suggesting that honey bees, like many other organisms, stand to benefit in their anti-pathogen responses from improved nutrition.

Parasites and pathogens affect bee nutrition

Pathogen infection and susceptibility is affected by the nutrition of the host, but also can contribute to the malnourishment itself. This phenomenon can take two forms in honey bees — infection affecting physiological nutrition via digestion and effects on behavior that impact hive level nutrition. *Nosema apis* and *N. ceranae* infect the gut, robbing bees of nutrients and causing digestive problems that can reduce lifespan [35]. *N. ceranae* also has the ability to cause immunosuppression in their honey bee hosts [36,37]. Because mortality associated with *Nosema* is exacerbated by lower quality pollen diet [31••], high *Nosema* loads, with accompanying malnutrition and immunosuppression could result in a feedback loop resulting in a higher incidence of pathogen-induced mortality. This malnourishment also has the potential to affect susceptibility to other pathogens; with reduced nutrition and immunity, honey bees may become more prone to normally-tolerable levels of virus infection. Co-infection with multiple pathogens has been frequently observed in weak or sick hives (e.g. in studies of 'colony collapse disorder' [22], and malnutrition could be part of this phenomenon.

Pathogen infection may also affect the nutritional health of individuals and colonies through behavioral perturbation that changes colony-level nutrition. Both *Nosema* and sacbrood virus (SBV) infection have been linked to reduced pollen collection [38], and *Nosema* can lead to reduced levels of the storage protein vitellogenin, and increased juvenile hormone levels, resulting in early onset of foraging behavior [25].

Varroa mites are considered the main pest threat to honey bees today. Their parasitization of developing pupae results in smaller bees with lower hemolymph volumes [18], and also results in the transmission of multiple viruses [39]. Further, Varroa infestation has been linked to a reduction in colony-level lipid stores [12], and high pollen stores have been linked to reduced Varroa infestation [40], again showing how a pest/pathogen complex can reduce group nutrition, though it is unclear the mechanism by which this reduction occurs. However, because Varroa is so tightly linked to the viruses it vectors, it is not yet clear whether nutritional deficits are caused by the mites themselves, or whether viral infection per se may also influence honey bee nutrition. Like *Nosema*, some viruses penetrate their hosts at the gut interface [41], raising the possibility that the viruses themselves could disrupt gut physiology, digestion, and/or nutrient acquisition.

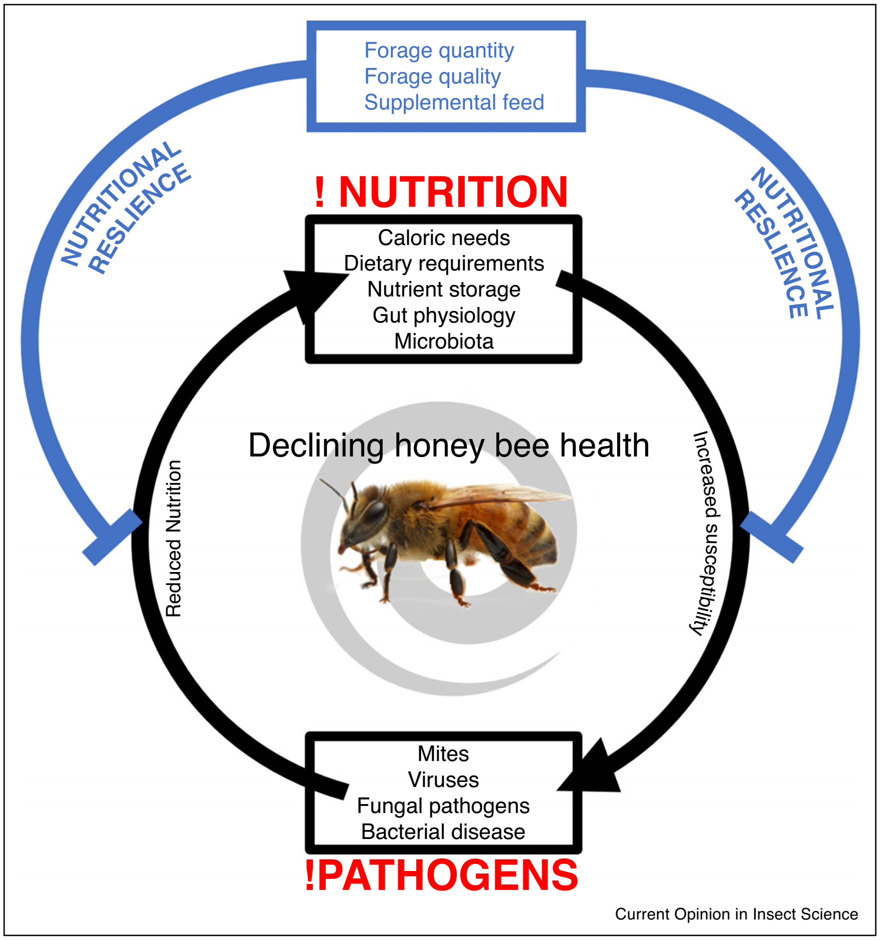
In summary, there have been relatively few studies that have addressed the physiological consequences of pathogen infection in honey bees, but the emerging picture from studies to date suggest that many of the major honey bee pathogens and pests can have negative impacts on bee nutrition.

Synthesis: feedbacks between nutrition and disease

In the wake of serious concerns about declining honey bee health over the past several decades, both nutritional and pathogen stress have intensified simultaneously. In many areas of the world, recent years have seen increasing transformation of landscapes into intensively managed crops that provide little forage for bees. This has had some of the largest impact in areas where forage was once plentiful [42•]. Thus, some managed honey bees have experienced massive shifts in food availability and diversity just in the last few decades. At the same time, there has been increased stress from pathogens due to globalization and Varroa pressure, with pathogenic virus strains spreading quickly [2,43] and the introduction of a new form of *Nosema* [44].

The feedback between nutrition and pathogens has the potential to create a cycle of stress that could have major impacts on bee health (Figure 1). As reviewed above, poor nutrition can leave bees more susceptible to infections, resulting in disease losses that could be recoverable under better dietary conditions. Some pathogen infections interfere with nutrition, burning up reserves or interfering with digestion. As co-infections of multiple pathogens likely occur, there is even the capacity for even interactions between these — creating a network of pathogen and dietary stresses that can affect bees at the individual and colony levels. Both nutritional stress [45,46] and pathogen infection [25,26] have been associated with a premature onset of foraging behavior and associated physiological changes; it is possible that, together, these effects synergize and are amplified.

Figure 1



Feedbacks between poor nutrition and pathogens have the potential to lead to positive feedback loops that contribute to spiraling declines in honey bee health. Nutritional stressors include unmet caloric needs, insufficient levels of required micronutrients, low levels of stored nutrients such as fat, protein, and glycogen, imbalanced or suboptimal gut physiology, and lack of healthy microbiota. Pathogen and parasite pressures include Varroa mites, multiple pathogenic viruses, fungal infections such as *Nosema* sp., and bacterial diseases such as European and American Foulbrood. We suggest cultivating 'nutritional resilience' by increasing honey bee forage quantity and quality in the environment, as well as improved supplemental feeding formulations can help stop such harmful feedback loops. Multiple approaches to improving nutrition may interfere with this feedback, reducing susceptibility to pathogens and compensating for the effects that pathogens have on nutritional physiology. Honey bee photo by Alex Wild.

For example, recent studies, both modeling-based and empirical, suggest that the interaction between multiple stressors such as nutritional stress and pathogen infection can lead to imbalances in colony division of labor, which may explain some instances of colony abandonment, one of the main symptoms of the mysterious 'colony collapse disorder' [32,47•].

What possible solutions can there be in the face of these severely interacting stressors? Treatments and preventatives for pathogens, particular viruses, are challenging. High levels of virus infection are usually linked to infestation with Varroa mites [18] and therefore monitoring and treatment of mite infestations is critical to preventing overwhelming virus levels. Once infected, however, there are no marketed treatments for virus infection in bees, though there has been some demonstration of a possible approach involving RNA-interference [48]. *N. ceranae* can be treated with an antimicrobial agent, but reoccurrence is common [26]. There is also variability in the legality of different treatments across the world, with some nations banning the use of antibiotics, thus systematic solutions to treating honey bee pathogens remain problematic.

Because pathogen detection and treatment can be challenging, another approach is to specifically target solutions for improving bee nutritional health. We suggest a multi-pronged effort for fostering 'nutritional resilience' to stress in managed honey bees that can be key factor in addressing bee health. With improved baseline nutritional health, bees will not only be less susceptible to feedbacks with pathogens, but good nutrition may also improve bees' responses in the face of other stressors including pesticide exposure [49] and management stress associated with migratory beekeeping practices [50,51]. What can be done to foster nutritional resilience in honey bees?

First, bee nutrition can be addressed on a landscape scale. Because honey bees have large foraging ranges, bees rely on a wide landscape to access the nutritional resources that help them thrive and therefore also rely on how humans manage vast amounts of land. For example, in just over a decade millions of acres of conservation land were removed from the United States' Conservation Reserve Program (CRP) and transformed into agricultural production [42•,52]. This rapid reduction in natural or naturalized landscapes results in nutritional deprivation that is not easily remedied by beekeepers. However, beekeepers do have some control over choice of apiary location with respect to landscape (and associated forage). Landscape features that may be desirable for apiary locations to maximize nutritional benefits include consideration not only of quantity of bee forage, but also forage diversity (improved by presence of native vegetation or pollinator plantings such as hedgerows, prairie restorations, etc.), nutritional quality of specific plants [53••], as well as seasonal availability of forage, which can be especially critical in fall as bees prepare for overwintering. One particular challenge, however, is that little empirical evidence exists showing how landscape restoration or management for pollinator conservation actually affects bee health. Moving forward, more studies using a 'landscape physiology' approach, which has shown promise for improving honey bee health through floral landscape enrichments in France [9], could be used to evaluate how landscape management regimes and strategies can improve bee nutritional physiology and health. We suggest it will be useful to develop guidelines, recommendations, and tools for improving apiary site selection to optimize forage benefits, recognizing this must be done on a regional basis because of large differences in habitat and forage composition across the global range of honey bees.

Second, bee nutritional needs can be better served through improved dietary supplementation. There has been increasing interest and development of improved artificial feed for bees, particularly the development of a variety of pollen supplements. However, it is still unclear what the precise dietary needs of bees are, and these needs are likely to be highly variable depending on seasonal conditions and environmental stressors. Diets that provide the best antiviral properties, for example, may not provide the best brood rearing properties. To improve supplemental feeding, more baseline information is needed on bees' basic nutritional needs, including requirements for essential micronutrients in addition to proper balancing of macronutrients [3,5,52]. There is also an increasing appreciation of the role of microbiota in the bee gut as well as in bee bread for maintaining proper nutritional health in honey bees [54]. Thus, improved supplemental feed in the future should aim to incorporate micronutrient requirements and microbiome composition, with a more nuanced understanding of honey bee nutritional requirements, including an increased awareness that such requirements may depend on colony life stage and season [31••].

While supplemental feeding is a reality in modern beekeeping, and can play a key role in keeping honey bees healthy during a foraging dearth, it is not an economical or sustainable solution to solving challenges of honey bee nutrition in changing landscapes. Although honey bees are not a native species to the Western hemisphere, and are not truly wild in much of the rest of the world, they still can benefit from conservation programs incorporating natural forage into agricultural landscapes. Hopefully, there can be more efforts from the public sphere to incentivize incorporating these into our landscapes, particularly in systems where there are proven benefits to water quality, soil sustainability, and pest control via natural enemies [55•]. Importantly, increasing natural forage for honey bees has the potential to also benefit native, non-honey bee pollinators, which are critical players in native ecosystems highly important in pollination services [56]. Native bees, while not discussed here, are likely to suffer from many of the same nutritional and pathogen challenges as honey bees; thus, increasing bee forage availability stands to improve the nutritional resilience of pollinator populations at large. Overall, all bees continue to face stress from multiple directions, and it seems unlikely that the global spread of pests and pathogens or agricultural intensification will disappear. Therefore, bee health may be best served by approaches that use targeted improvements in the landscape to improve nutrition in an attempt to buffer bees against other stresses.

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