RESEARCH ARTICLE

Parasites and pesticides act antagonistically on honey bee health

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Abstract

1. Pesticides and parasites have each been linked to increased mortality in western honey bees (*Apis mellifera*). Currently, it is uncertain if one makes the other worse; several studies have tested for potential synergistic stressor effects, but results have been mixed.

2. Here, we use a hierarchical meta-analysis of 63 experiments from 26 studies to gain a clearer view of the combined effects of parasites and pesticides on honey bee health.

3. We found that combined pesticide–parasite treatments do tend to be deadlier than uncombined treatments but are significantly less deadly than predicted additive or multiplicative effects. In other words, combined treatment effects are not synergistic, but antagonistic.

4. Much of the previous uncertainty about the combined effects of pesticides and parasites on honey bee health can be attributed to a bias in the previous research against stressor antagonism; many researchers have excluded the possibility of antagonism a priori.

5. *Synthesis and applications*. Meta-analysis shows that when honey bees are stressed by a combination of pesticides and parasites, the combined stress effect is antagonistic, that is, less than the sum of its parts. A better understanding of the mechanisms underlying this antagonism could prove critical for effective management of honey bee health.

KEYWORDS
colony loss, honey bee, interaction, meta-analysis, parasite, pesticide, stress, synergy

1 | INTRODUCTION

Few species are more vital to modern agriculture than western honey bees *Apis mellifera*. They produce valuable commodities such as honey, beeswax and propolis, and, more importantly, they provide the lion's share of worldwide crop pollination services, which have been valued at €153 billion (Gallai et al., 2009). Recent overwintering colony losses in the United States have been alarming. Since 2010, mortality rates have consistently been above 20%, reaching 37.7%

in the winter of 2018–2019 (Bruckner et al., 2018). Increased mortality has also been reported in Europe (Brodschneider et al., 2018; Gray et al., 2019). This has reduced the profitability of bee keeping, and threatens the sustainability of agricultural systems that rely on honey bee pollination.

Declines in honey bee populations appear to have multiple causes (Potts et al., 2010; Ratnieks & Carreck, 2010), the most important of which are increased exposure to parasites and pesticides. The most troublesome parasites have been microsporidian

species in the genus *Nosema,* and the mite species *Varroa destructor.* Infections by *Nosema* spp. degrade honey bee midgut integrity and immune response (Paris et al., 2018), while Varroa mites feed upon immature bees and vector several debilitating viruses (Ramsey et al., 2019). As the prevalence of these parasites has increased, so too has honey bee exposure to pesticides (Goulson et al., 2015; Wintermantel et al., 2020). Managed honey bee colonies are often chronically exposed to sublethal doses of pesticides, so much so that pesticide residues are frequently detected in bee products (Mitchell et al., 2017; Mullin et al., 2010). Chronic pesticide exposure can impede development (Friedli et al., 2020; Tomé et al., 2020), impair behaviours such as learning, foraging and homing (Aliouane et al., 2009; Yang et al., 2008), and increase overall mortality rates (Rondeau et al., 2015). In sum, much of the recent increase in honey bee mortality can be traced to increases in parasite and pesticide prevalence.

Of course, in the field, honey bees can face multiple stressors simultaneously (Little et al., 2015; Shutler et al., 2014), which raises the possibility of a variety of interactions between stressors. In the simple additive case, the combined effect of parasites and pesticides would be the sum of their individual effects, for example on instantaneous mortality rates. If mortality is measured as the proportion of dead bees in a finite sample of individuals, it makes more sense to express additive effects on a logarithmic scale; otherwise, the predicted additive mortality effect could be >100% (Sih et al., 1998). This logarithmic additive effect is commonly referred to as the predicted multiplicative effect (Côté et al., 2016). Two other possibilities are that stressors combine synergistically, in which case their combined effects are greater than the expected additive or multiplicative effect, or the stressors combine antagonistically, in which case their combined effects are less than the expected additive or multiplicative effect. This classification of stressor interactions could have management implications. Synergistic interactions are thought to reduce the resiliency of a system, and thus could motivate more aggressive and expensive interventions (Côté et al., 2016), whereas antagonistic interactions raise the possibility of mitigating effects between stressors, in which case reducing one stressor could actually be harmful overall (Brown et al., 2013).

Although several types of stressor interaction are possible, the research on how pesticides and parasites affect honey bee heath has focused almost exclusively on potential stressor synergies (e.g. Collison et al., 2016; Sánchez-Bayo et al., 2016). This bias is not without a basis. In addition to the adverse health effects mentioned previously, exposure to sublethal doses of pesticides can impair honey bee immune function by reducing antimicrobial capacity, delaying wound healing and lowering the number of circulating haemocytes (Brandt et al., 2017; James & Xu, 2012). Moreover, pesticides can disrupt health-promoting behaviours such as grooming, hive cleaning and foraging (Henry et al., 2012; de Mattos et al., 2017; Yang et al., 2008). But there is also a basis for expecting antagonism between stressors. Broad surveys of how multiple stressors affect the health of animal populations show that antagonism is as least as common as synergy (Brown et al., 2013; Côté et al., 2016; Darling

& Côté, 2008). And for honey bees, there is evidence of mitigating effects between pesticides and parasites: pesticide exposure can reduce the density of *Nosema* spp. in the midgut epithelium (Aufauvre et al., 2012; Gregorc et al., 2016). Thus, the bias against stressor antagonism in the honey bee health research may be unwarranted.

Studies of the interactions between stressors on honey bee health have had mixed results, with synergism detected in some studies but not in others, but, to repeat, previous studies have mostly ignored the possibility of stressor antagonism, and have inconsistently tested for significant non-additive interactions. Here, to improve our view of the effects of pesticide–parasite interactions on honey bee health, we use meta-analysis. Our primary objective is to estimate, across studies, if the effects of combined pesticide-parasite treatments are greater, less than, or indistinguishable from predicted additive or multiplicative effects. We also quantify the relative harm of single and combined stressors, and account for how measures of stress on honey bee health could depend on variations in experimental design.

2 | MATERIALS AND METHODS

To assemble a set of relevant studies, we conducted a literature search using the search parameters (bee* or honeybee* or bumblebee*) and (pesticide* or neonicotinoid* or neo-nicotinoid* or pesticide* or acaricide*) and (parasite* or nosema* or virus* or viral* or varroa* or mite*). Literature searches were conducted from 31 May to 17 June 2019 using Google Scholar and 12–13 August 2020 using Web of Science. Studies were also identified from the citations of three recent review articles and one meta-analysis on the interactions between pesticides and parasites on the health of *Apis mellifera* (Collison et al., 2016; Havard et al., 2020; O'Neal et al., 2017; Sánchez-Bayo et al., 2016).

To be included in our analysis, the study had to use a factorial experimental design where bees were exposed to (a) a control treatment without parasites or pesticides, (b) parasite treatments, (c) pesticide treatments and (d) combined pesticide–parasite treatments. In addition to chemicals that honey bees might encounter while foraging, we included pesticides that are typically used by beekeepers to manage Varroa mite infestations. From the abstracts of studies returned by the literature searches, we identified 102 candidate studies. After more careful review, 75 of these studies were excluded because they did not meet the criteria for inclusion, leaving 27 suitable studies. One more study was excluded because stressor effects on mortality were so high that detecting synergy would have been problematic. For citations, see the Data Sources section. Further details on the search are presented as a PRISMA flow diagram (Moher et al., 2009) in Figure S1.

Studies testing for interactions between pesticides and parasites examine a wide variety of health-related variables, including honey bee mortality, gene expression, behaviour, body size and fecundity. We focused on mortality, as it was the most commonly used variable and varied least in how it was measured and reported. We only included studies on the worker cast, as too few

studies have been done on queens or drones. Since most of the 26 studies included multiple experimental observations, and since each factorial experiment measured three experimental effect sizes (pesticide-only, parasites-only and combined pesticide–parasite treatments), the total number of measured effect sizes was 189. Where possible, experimental effects were taken from the original text and tables. Otherwise, data were extracted from graphs with the R (R Core Team, 2019) package METADIGITISE (Pick et al., 2019).

To account for variation in experimental design, we also recorded (a) the identity of focal pesticides and parasites, (b) the number of days from the onset of stress to the time of mortality measurement, (c) the life stage (immature or adult) of bees at the beginning of the treatment and (d) whether bees were housed in hives or in cages. There were insufficient replicates of specific pesticides and parasites to include each as a level in a predictive factor, so pesticides were classified as either neonicotinoid pesticides or non-neonicotinoid pesticides. We were not able to model the effect of pesticide dose, as it was inconsistently reported and is difficult to quantify when mixed with sucrose and provided ad libitum, as was true of many experiments.

Stressor synergism and antagonism are determined relative to a predicted additive effect. As mentioned previously, for a mortality response expressed as the proportion of dead individuals in a finite sample, the use of a predicted multiplicative effect (Table S1) as the threshold between synergy and antagonism avoids the problem of predicted mortalities >100% (Côté et al., 2016). But choosing between predicted additive and multiplicative effects can depend more generally on which null model is a better match to the biological dynamics at hand. Predicted additive effects are better suited for stressors with non-overlapping modes of action and for systems without strong density dependence, whereas the opposite applies to predicted multiplicative effects (Hay, 1996). The choice of predictive effect can also depend on the particular hypothesis being tested; since predictive additive effects are invariably greater than predictive multiplicative effects, the use of a predicted additive threshold results in a more conservative test for synergy (and a more liberal test for antagonism). Given these considerations, along with gaps in our understanding of how pesticides and parasites might interact to affect honey bee health, we repeated our analyses with each predicted effect type.

Predicted effects were calculated from the proportion of mortality in pesticide-only and parasite-only treatments. The predicted additive is the sum of these proportions, while the predicted multiplicative is the sum of the proportions minus the product of the proportions. To avoid nonsensical predicted additive effects, we examined only experimental observations taken before the summed mortality proportions of individual stressors reached 100%. As mentioned above, this forced us to drop one study from the analysis (Grassl et al., 2018), since only data from the end of the experiment were reported. For consistency, these same data were analysed in models with predicted multiplicative effects. All effect sizes, both real and predicted, were converted

into log risk ratios and variances using the R package METAFOR (Viechtbauer, 2010; Table S1).

Fixed-effect predictor variables, referred to as moderators in a meta-analysis, were selected based on an exploratory analysis using the R package MuMIn (Bartoń, 2019). These were (a) *treatment type*, a binary variable that distinguished between observed combined treatment effects and predicted additive or multiplicative effects; (b) *trial duration*, measured in days and mean-centred; (c) *parasite type*, a factor with levels for *Nosema* spp., viruses, bacteria or Varroa mites; (d) *pesticide type*, a binary variable that distinguished between neonicotinoid and non-neonicotinoid pesticides; (e) *accommodation type*, that is, whether bees were housed in cages or in hives and (f) *life stage*, a binary variable the distinguished between adult and immature bees. Variance inflation tests did not indicate significant multicollinearity between moderators. In addition to these fixed effects, study and trial were included as nested random effects, as the majority of studies included multiple trials and multiple effect observations from each trial.

The two models, additive and multiplicative, were fit using the rma.mv function in *metafor* (Viechtbauer, 2010), with test statistics of the individual coefficients based on a *t*-distribution, similar to the Knapp and Hartung method (Hartung & Knapp, 2003; Viechtbauer, 2010; Viechtbauer et al., 2015; Code S1). Each of the models had a total of 126 effect sizes, the sum of 63 observed combined treatment effects and 63 predicted additive or 63 predicted multiplicative effects (Figure S2). To test for significant differences in mortality effects from different parasite classes—the only multistate discrete fixed effect predictor variable—we used the R package MULTCOMP (Hothorn et al., 2008), with the Holm adjustment to correct for multiple-testing *p* value inflation (Holm, 1979).

We also fit a model to get a sense of the relative magnitudes of the main effects of the single and combined stressors. The main fixed and random effects in this model were the same as in the main analyses, except that the pesticide and parasite type variables were excluded (since some treatments lacked one or the other), and the *treatment type* was a factor with three levels: pesticide-only treatments, parasite-only treatments and combined-stressor treatments. No multicollinearity was detected between moderators. This model had a total of 189 effect size observations, 63 from each single-stressor treatment and 63 from the combined treatment. Pairwise comparisons between treatments were conducted using the R package MULTCOMP with the Holm adjustment (Code S1).

We ran several tests of model fit and bias. To test for publication bias, which occurs when significant results are more likely to be published than non-significant results, we used a version of Egger's test (Egger et al., 1997), implemented in the R package METAFOR and modified for hierarchical multivariate analyses. We performed this test on the combined versus single stressors model, as it did not contain predicted—that is, unobserved—additive or multiplicative effects. We failed to reject the null hypothesis of no bias (*p* value = 0.14). We tested for outliers using Cook's distance (Cook, 1977), as implemented in the R package METAFOR. These tests only suggested disproportionate influence in our single versus

multiple stressors model, and so we carried out a leave-one-out analysis for that model (Figures S3–S6). We also quantified effect heterogeneity across studies. Rather than using Cochran's Q, which has low power to detect heterogeneity in hierarchical mixed models when the number of studies is small (Gavaghan et al., 2000), we used an I^2 test, following Nakagawa and Santos (2012), with code provided by Viechtbauer (2019). This estimates the relative proportions of between-study to within-study effect size variance (Table S2).

For ease of interpretation, after model coefficients and confidence intervals were estimated, they were transformed back to risk ratios. Hence, reported confidence intervals are asymmetric. Risk ratios express the multiplicative increase or decrease of risk of events between treatments (Higgins et al., 2019). A risk ratio of one indicates no effect; a risk ratio of <1 indicates a decrease in mortality and a risk ratio of >1 indicates an increase in mortality.

3 | RESULTS

3.1 | Comparison of combined and predicted *additive* effects

We found a significant difference between the mean combined treatment effect and the predicted additive effect of parasites and pesticides on honey bee mortality: the combined treatment was 1.44-fold (1.37–1.44 ±95% CI; p value < 0.001) less likely to cause mortality than the predicted additive effect (Figure 1). This interaction between pesticides and parasites is antagonistic.

Trial duration also had a significant effect, with the risk of mortality decreasing by 1.04-fold per day (1.02–1.07 ±95% CI; p value = 0.002). As trial duration ranged from 3 to 25 days, our findings suggest that the risk of mortality was 2.40-fold less likely at 25 days than at 3 days. We also found a significant interaction
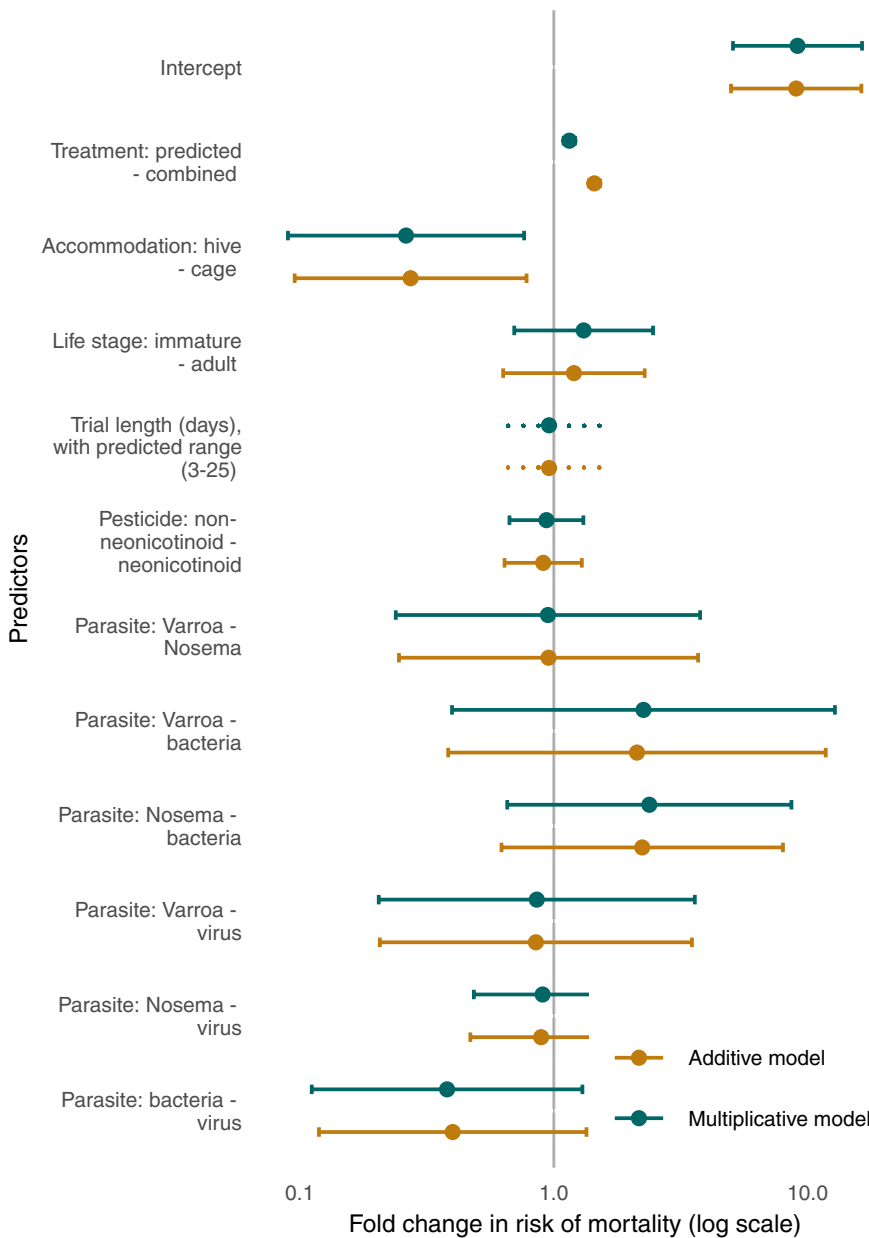

FIGURE 1 Effects of predictor variables on the relative risk of mortality of honey bees in additive and multiplicative models. The *x*-axis represents the relative risk of predictors on mortality and is on a log scale. Horizontal bars represent ±95% CI. Effects >1 indicate an increased risk of mortality; effects <1 indicate a decreased risk. For binary variables, the first state listed is the basis for comparison. For example, for the 'treatment variable', the predicted combined effects are the basis for comparison; thus, effects >1 indicate the observed combined effects are more harmful, that is, that the interaction is antagonistic. Pesticide category 'mixed' is not shown. The effect of trial length was estimated on a per-day basis; dotted horizontal lines show how such effects accumulate from the 3rd (right side of line) to 25th (left side) days of a trial

between treatment and accommodation types: keeping bees in hives, rather than in cages, decreased the risk of mortality by 3.51-fold (1.30–9.49 ±95% CI; *p* value = 0.014). However, this may be influenced by uneven sample sizes; in the vast majority of experiments, bees were in cages rather than hives (114 cage effects vs. 12 hive effects). We found no significant differences in the effects of different parasite kinds, between neonicotinoid and non-neonicotinoid pesticides (*p* value = 0.59), or between immature and adult worker bees (*p* value = 0.57; Figure 1; Table S3).

3.2 | Comparison of combined and predicted *multiplicative* effects

Results with predicted multiplicative effects were much the same as they were with predicted additive effects; combined treatments were 1.15-fold (1.09–1.21 ±95% CI; *p* value < 0.001) less likely to cause mortality than the predicted multiplicative effect (Figure 1). The effects of trial duration, accommodation, and pesticide and parasite type were also similar to what we found with predicted additive thresholds. Trial length had a 1.04-fold (1.02–1.07 ±95% CI; *p* value = 0.001) decrease in mortality per day, and bees treated in hives had a 3.66-fold (1.33–10.1 ±95% CI; *p* value = 0.012) decrease in risk of mortality compared to bees treated in cages. No other results were significant (Figure 1; Table S4).

3.3 | Comparing single and multiple stressor effects

Although combined pesticide–parasite effects tended to be antagonistic, they were nonetheless significantly more deadly than single-stressor treatments (Table S5). On average, combined treatments were 1.29-fold (1.21–1.37 ±95% CI; *p* value < 0.001) more likely to cause mortality than parasite treatments, and 1.54-fold (1.44–1.65 ±95% CI; *p* value < 0.001) more likely to cause mortality than pesticide treatments. Also, parasite treatments were 1.20-fold (1.19–1.28 ±95% CI; *p* value < 0.001) more likely to cause mortality than pesticide treatments. All treatments significantly increased the risk of mortality when compared to controls: parasite treatments increased the likelihood of mortality by 5.44-fold (3.49–8.48 ±95% CI; *p* value < 0.0001), pesticide treatments increased the likelihood of mortality by 4.54-fold (2.91–7.08 ±95% CI; *p* value < 0.0001) and the combined treatment increased the likelihood of mortality by 7.00-fold (4.50–10.91 ±95% CI; *p* value < 0.0001, Figure 2).

As for the other predictors, we again found a significant effect for trial duration—the risk of mortality decreased by 1.05-fold (1.02–1.07 ±95% CI; *p* value = 0.0004) per day of the experiment. We also found that bees housed in hives had a 3.02-fold (1.37–6.66 ±95% CI; *p* value < 0.007) decreased likelihood of mortality when compared to bees housed in cages. There was no significant result for life stage (*p* value = 0.40; Figure 2; Table S5).
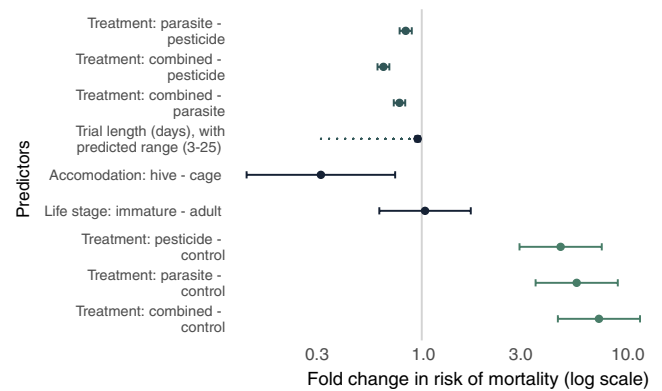

FIGURE 2 Effects of pesticides, parasites and combined treatments on the relative risk of mortality of honey bees, along with the effect of other predictor variables. The *x*-axis shows the relative risk of predictors on mortality and is on a log scale. Horizontal bars represent ±95% CI. To improve readability, the model was fit without an intercept. Values >1 indicate an increased risk of mortality and <1 indicate a decreased risk. Shown are pairwise comparisons between treatments, and between treatments and controls. The effect of trial length was estimated on a per-day basis; dotted horizontal lines show how such effects accumulate from the 3rd (right side of line) to 25th (left side) days of a trial. There were 26 studies and 189 effect sizes included in this model

4 | DISCUSSION

This meta-analysis shows that pesticides and parasites tend to act antagonistically on the health of honey bees. This antagonism is significant and robust to variation in experimental approaches. It is also robust to whether the predicted combined linear effect is additive or multiplicative. And yet none of the studies that we meta-analysed had reported pesticide–parasite antagonism. One explanation for this is that researchers have tended to exclude antagonism a priori. Indeed, in more than 75% (20/26) of the analysed studies, authors make no mention of the possibility of stressor antagonism. Moreover, in 10 studies, there was no explicit statistical test of non-additive stressor interactions. It could also be that single studies have lacked statistical power, as non-additive interactions take more statistical power to detect than main effects (Slinker, 1998).

To get a sense for how variation in statistical power might have skewed the view of how combinations of parasites and pesticides affect honey bee health, we re-analysed individual studies. For each study, we compared the difference between the observed combined effect and the predicted additive or multiplicative effects to a null distribution of such differences generated through non-parametric bootstrapping (see Code S2 for details). Using both predicted additive and multiplicative effects, we found significant antagonism in studies which did not report it. With the multiplicative model, which is more conservative for antagonism, we found pronounced antagonism in 19 out of 63 trials, in 10 studies. With the additive model, which is more conservative for synergism, we found antagonism in 28 out of 63 trials, in 15 studies (Figure 3; Table S6). Thus, the previous lack of evidence in support of pesticide-parasite antagonism
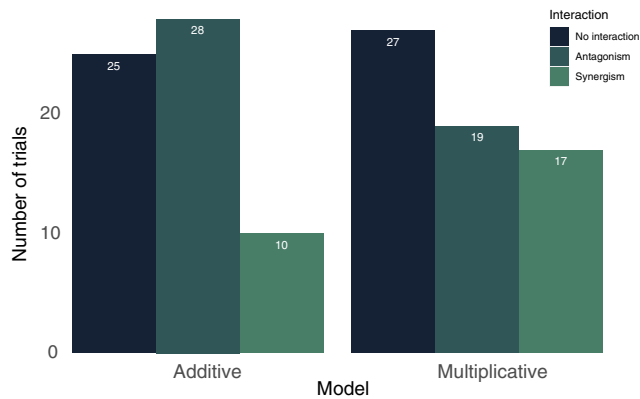
FIGURE 3 Reanalysis of individual studies of the interactions between parasites and pesticides on honey bee health. We used non-parametric bootstrapping to assess the significance of the observed difference between combined treatment effects and predicted additive and multiplicative effects. An interactions were considered antagonistic when a combined effect was significantly less than a predicted effect, and synergistic when a combined effect was significantly greater than a predicted effect. In all, 63 trials from 26 studies were included, detailed results in Table S6

on honey bee health cannot be attributed solely to a lack of single-study statistical power.

One counter-intuitive effect estimate from our meta-analysis warrants a brief consideration: increasing trial duration reduced mortality. As a reminder, the trial duration variable was the number of days from the start of an experiment until the experiment ended or the sum of individual-stressor effects exceeded 100%. The most likely explanation of this effect is that the causal relationship runs in the opposite direction, and that more lethal parasite and pesticide treatments resulted in shorter trial durations.

It is important to point out that most of the published research has been on small groups of bees kept in laboratory cages and isolated from the rest of their colony; relatively few studies have been of intact hives. Given the degree of interdependence within a honey bee colony and the potential of intact colonies to buffer against stress (Henry et al., 2015; Osterman et al., 2019; Straub et al., 2015), this strains the mapping of experimental effects to what may happen in field conditions. The cages used in experiments on individual bees are likely to be stressors themselves (Williams et al., 2012, 2013), as caged bees are prevented from performing many normal behaviours that could exacerbate the effect of other stressors. Caged bees could also be prevented from excreting toxins during cleaning flights—as may happen in field situations (Coulon et al., 2018). In our analysis, bees kept in cages had more than three-fold the risk of mortality when compared to bees kept in hives. But we had many more effect sizes for experiments on bees treated in cages (114 in our predictor analyses, 171 in our single versus multiple stressor analysis) than for bees treated in hives (12 in our main analysis, 18 in our single versus multiple stressor analysis).

In the meta-analysed studies, 39 experiments tested the effects of neonicotinoid pesticides, 22 tested the effects of non-neonicotinoid pesticides and two tested a combination of neonicotinoid and non-neonicotinoid pesticides. We found no significant difference between the two pesticide classes. We cannot rule out that this stems from consistent between-class differences in experimental doses, as information about doses were insufficient. But since most studies attempted to expose honey bees to field-realistic levels, this seems unlikely.

What is the mechanistic basis of the antagonism between pesticides and parasites on honey bee health? We see two main possibilities. The first possibility is mitigation, whereby one stressor ameliorates the effects of another. An example mentioned previously is pesticides reducing the intensity of infections by *Nosema* spp. (Aufauvre et al., 2012; Gregorc et al., 2016). If this is the case, then reducing pesticide exposure could actually be detrimental to honey bee health, although we found no evidence of this. The second possibility is tolerance induction, whereby one stressor activates a plastic stress-compensation phenotype that confers resistance to a broad array of stressors (Vinebrooke et al., 2004). For example, both pesticide exposure and parasite infection can increase oxidative stress and induce generalized physiological mechanisms for restoring redox homeostasis (Kodrík et al., 2015)). Of course other mechanisms are possible, but none that occur to us seem as likely.

In conclusion, on average, when honey bees are exposed to parasites and pesticides in concert, their combined effects are antagonistic, and a clear view of this has heretofore been hindered by a systematic bias in the research community against multi-stressor antagonism. More research is needed to evaluate how living in hives can ameliorate stress, and more routine and consistent quantification of pesticide dose would also be useful. As it stands, the physiological mechanisms underlying this antagonism are unclear, but different possibilities would have different management implications. Thus, sound interventions to diminish honey bee mortality may hinge on an improved understanding of the ecology and physiology of the interactions between honey bees, pesticides and parasites. At the very least, now we know that antagonism is what we need to understand.

AUTHORS' CONTRIBUTIONS
G.B. conceived of the study, collected the data, carried out the analysis and wrote the first draft of the paper; G.R.W. assisted with study design; A.E.W. and N.B.H. assisted with analyses. All authors contributed critically to the drafts and gave final approval for publication.

DATA AVAILABILITY STATEMENT
Data available via Github https://github.com/birdoptera/Honey_bee_antagonism (Bird et al., 2020).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.