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Agrochemicals interact synergistically to increase bee mortality

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Harry Siviter[1,2,6]✉, Emily J. Bailes[1,3,4,6], Callum D. Martin[1], Thomas R. Oliver[1,4,5], Julia Koricheva[1], Ellouise Leadbeater[1] & Mark J. F. Brown[1]

Global concern over widely documented declines in pollinators[1–3] has led to the identification of anthropogenic stressors that, individually, are detrimental to bee populations[4–7]. Synergistic interactions between these stressors could substantially amplify the environmental effect of these stressors and could therefore have important implications for policy decisions that aim to improve the health of pollinators[3,8,9]. Here, to quantitatively assess the scale of this threat, we conducted a meta-analysis of 356 interaction effect sizes from 90 studies in which bees were exposed to combinations of agrochemicals, nutritional stressors and/or parasites. We found an overall synergistic effect between multiple stressors on bee mortality. Subgroup analysis of bee mortality revealed strong evidence for synergy when bees were exposed to multiple agrochemicals at field-realistic levels, but interactions were not greater than additive expectations when bees were exposed to parasites and/or nutritional stressors. All interactive effects on proxies of fitness, behaviour, parasite load and immune responses were either additive or antagonistic; therefore, the potential mechanisms that drive the observed synergistic interactions for bee mortality remain unclear. Environmental risk assessment schemes that assume additive effects of the risk of agrochemical exposure may underestimate the interactive effect of anthropogenic stressors on bee mortality and will fail to protect the pollinators that provide a key ecosystem service that underpins sustainable agriculture.

Conventional intensive agriculture is not only associated with landscape simplification and habitat loss, but also relies heavily on agrochemicals (including pesticides, insecticides, herbicides and fungicides) to control pest species and enhance yield[10,11]. Individually, these factors negatively affect the providers of key ecosystem services and—in particular—the insects that underpin crop pollination[4]. In addition, the use and transport of commercial pollinators, such as domestic honeybees (*Apis*) and commercially produced bumblebees (*Bombus*), at high densities and across great distances, increase pathogen pressure on both wild and managed pollinators in these agro-ecosystems[12]. As a consequence, key pollinators—such as social and solitary bees—will frequently be exposed to a multitude of environmental stressors within agricultural environments[3,8].

When organisms are exposed to more than one stressor, the resulting effects can be: (1) antagonistic, in which the effect of both stressors combined is less than would be predicted from adding the individual effects of each stressor together, which may occur when the stressors directly compete with one another or interact negatively within the target organism[13–15]; (2) additive, in which the effect of two stressors is equal to their combined individual effects, which is likely to occur when stressors affect different aspects of the biology of the target organism[16]; (3) synergistic, in which the effect of combined stressors is significantly higher than predicted additive effects, perhaps because one stressor potentiates the other[17,18]. Although numerous narrative reviews have suggested that bee population declines may be driven by the accumulative (additive or synergistic) negative effects of multiple anthropogenic stressors on bees[3,8,19], empirical studies have demonstrated a range of interaction effect types[19–21], making it unclear how these effects should be modelled when considering management interventions. Understanding the interactions between stressors is vital for pollinator conservation as it enables policy-makers to implement effective mitigation measures within the risk assessment process to reduce the negative consequences of anthropogenic stressors on bees. Here, we present a meta-analysis of the interactive effects of environmental stressors on bees. Specifically, we address the following questions. (1) Whether interactions between environmental stressors have an overall synergistic effect on bee mortality and/or other fitness proxies; (2) whether specific types of environmental stressors interact in a way that is more detrimental than others; and (3) if these interactions occur, what mechanisms drive any observed differences.

To determine how different environmental stressors interact and affect pollinator health, we conducted a systematic search of published studies on the effects of anthropogenic stressors that are thought to be the greatest drivers of bee declines[3,8,12]. We searched Web of Science

[1]Department of Biological Sciences, Royal Holloway University of London, Egham, UK. [2]Department of Integrative Biology, University of Texas at Austin, Austin, TX, USA. [3]Department of Molecular Biology and Biotechnology, University of Sheffield, Sheffield, UK. [4]School of Natural Sciences, Bangor University, Bangor, UK. [5]Rothamsted Research, Harpenden, UK. [6]These authors contributed equally: Harry Siviter, Emily J. Bailes. ✉e-mail: Harry.Siviter.2016@live.rhul.ac.uk

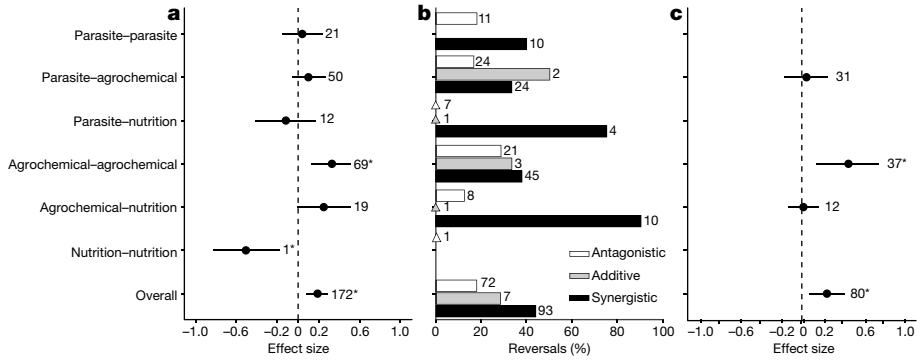

Fig. 1 | The interaction effects of parasites, agrochemicals and nutritional stressors on bee mortality. a, The effect sizes for the indicated interaction effects. Data are Hedges' *d* values ± 95% CI. Interactions are synergistic when the effect size is positive and the 95% CI does not include zero, antagonistic when the effect size is negative and the 95% CI does not include zero, and additive when the 95% CI includes zero. Numbers next to the 95% CIs indicate the number of effect sizes in each category. Asterisks indicate that the 95% CI does not include zero. **b**, The percentage of additive, antagonistic and synergistic interactions between stressors that were reversal interactions (Methods). The fill colour of the bars indicates the type of interaction. Triangles indicate interactions for which there were no reversals. Numbers indicate the total number of effect sizes within that category. **c**, Effect sizes (Hedges' *d* values ± 95% CI) for analyses in which bees are exposed to field-realistic concentrations of agrochemicals.

for studies that assessed how exposure to agrochemicals, parasites and poor nutrition interact to influence bee health (see Methods for search terms and further details), obtaining 14,844 papers. To be included in our analysis, bees had to be exposed to at least two environmental stressors in a fully crossed design (that is, control group, treatment 1, treatment 2 and treatments 1 + 2). We also included studies in which two stressors from the same class were used (for example, more than one agrochemical). The response variables were classified into five separate categories: (1) mortality, (2) fitness proxies (for example, reproductive output or colony growth), (3) behaviour, (4) parasite load and (5) immunity (see Supplementary Table 1 for category definitions). Across the five different categories of response to environmental stressors, we obtained data from 100 papers published between 1991 and 2020.

We then calculated the observed interaction effect as the standardized mean difference (Hedges' *d*) between the predicted value that would be seen if the stressors acted additively ((mean stressor 1 − mean control) + (mean stressor 2 − mean control) + mean control)), and that would be observed when both stressors are used in combination (mean of the combination of stressor 1 + stressor 2)[22,23]. For effects that are expected to be positive (for example, effects of stressors on parasite load) a significant positive interaction effect would indicate a synergistic interaction, whereas a negative effect indicates antagonism, and zero values indicate additive effects (effects were considered significantly different from zero if their 95% confidence intervals (CIs) did not include zero). Conversely, for effects that are expected to be negative (for example, effects of stressors on the number of worker bees), the reverse is true. Therefore, in cases in which both main effects were negative, or in which the largest main effect was negative (Methods), we inverted the sign of the estimated interaction effect, such that significant positive and negative interaction effects indicated synergism and antagonism, respectively[22,23]. We removed from the analysis 10 studies (29 out of 385 effect sizes) for which the predicted additive effect of both stressors exceeded the boundaries of experimental observation (for example, more than 100% mortality), because the observed interaction effects from such studies are likely to produce unreliable estimates of the interaction effect size (Methods).

Overall, exposure to multiple stressors had a synergistic effect on bee mortality ($d = 0.19$, 95% CI = 0.08 to 0.29, $n = 172$) (Fig. 1a) and an additive effect on fitness proxies ($d = -0.06$, 95% CI = −0.32 to 0.20, $n = 39$) (Fig. 2a). Between-study heterogeneity for both bee mortality ($I^2 = 96.8\%$) and fitness proxies ($I^2 = 90.\%$) was high, with individual effect sizes demonstrating additive, synergistic and antagonistic interactions between stressors (Fig. 1b and Extended Data Fig. 1). We investigated this heterogeneity by examining the potential differences between stressor group combinations (for example, parasite × parasite or agrochemical × nutrition) and found that these did not explain the heterogeneity for either dataset (mortality, QM (test of model coefficients) = 8.26, d.f. = 5, $P = 0.14$; fitness proxies, QM = 3.30, d.f. = 5, $P = 0.65$). However, subgroup analysis revealed that the strongest evidence for synergistic effects on bee mortality derived from those studies in which bees were exposed to multiple agrochemicals (agrochemical × agrochemical, $d = 0.33$, 95% CI = 0.13 to 0.52, $n = 69$) (Fig. 1a).

By contrast, we found no evidence to suggest that the overall interaction effects differed from additive expectations for the effects of stressor combinations that involved parasite infection or nutrition on mortality (parasite × parasite, $d = 0.04$, 95% CI = −0.16 to 0.24, $n = 21$; parasite × nutrition, $d = -0.12$, 95% CI = −0.42 to 0.17, $n = 12$) (Fig. 1a), including those in which such stressors were combined with agrochemicals (parasite × agrochemical, $d = 0.10$, 95% CI = −0.06 to 0.27, $n = 50$; agrochemical × nutrition, $d = 0.25$, 95% CI = −0.01 to 0.51, $n = 19$) (Fig. 1a). For parasite infections, this may reflect the qualitative differences in the effects of individual parasite groups and, accordingly, individual combinations demonstrated a range of antagonistic, synergistic and additive effects (Extended Data Fig. 2). However, we are cautious in our interpretation of this result; first, because the sample size for these subgroups was smaller than those involving agrochemical × agrochemical combinations and, second, because our analysis is inherently conservative in its ability to detect synergism for bounded response variables such as mortality. Where additive predictions approach the boundary of experimental observation (for example, 100% mortality), synergistic interactions may appear additive simply because there is very limited scope to exceed the additive prediction, whereas antagonistic interactions are unaffected.

To determine whether experimental doses of agrochemicals at above field-realistic levels (see Methods for a definition of this term) were driving the synergistic effects on bee mortality, we reanalysed our dataset including only field-realistic dosages in the analysis. When only experiments with field-realistic agrochemical exposure were analysed, the interaction effects between agrochemicals and nutritional stress or inoculation with parasites remained additive (agrochemical × nutrition, $d = 0.02$, 95% CI = −0.13 to 0.17, $n = 12$; parasite × agrochemical, $d = 0.05$, 95% CI = −0.16 to 0.26, $n = 31$) (Fig. 1c) and those involving multiple agrochemicals remained synergistic (agrochemical × agrochemical, $d = 0.46$, 95% CI = 0.15 to 0.76, $n = 37$) (Fig. 1c). Furthermore, when only field-realistic agrochemical data were included in the main analysis, the overall effect of all stressors also remained synergistic (bee mortality at field-realistic levels, $d = 0.25$, 95% CI = 0.08 to 0.43, $n = 80$) (Fig. 1c).

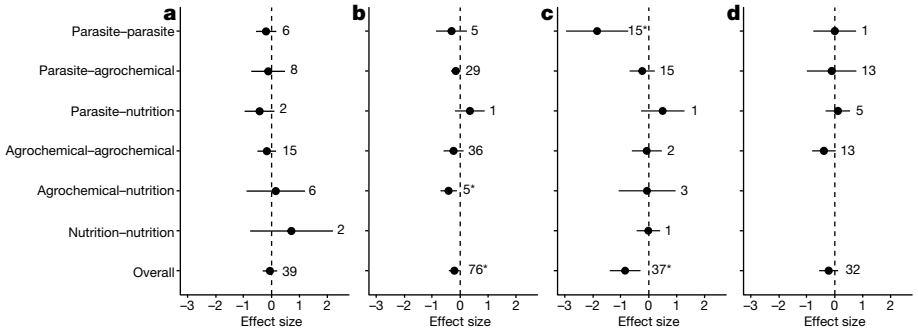

Fig. 2 | The interaction effects of parasites, agrochemicals and nutritional stressors on non-mortality response measures. **a**–**d**, Interaction effects of the indicated stressors on bee fitness proxies (**a**), behaviour (**b**), parasite load (**c**) and immune response (**d**). Data are Hedges' *d* values ± 95% CI. Interactions are synergistic when the effect size is positive and the 95% CI does not include zero, antagonistic when the effect size is negative and the 95% CI does not include zero, and additive when the 95% CI includes zero. Numbers next to the 95% CIs indicate the number of effect sizes in each category. Asterisks indicate that the 95% CI does not include zero. The scale is different to Fig. 1.

Both the mortality and fitness datasets had a strong bias towards honeybees (*Apis* spp.) (Extended Data Fig. 3); therefore, to explore the variation between different genera, we re-ran the analysis with data grouped by genus. As before, this identified an overall synergistic interaction between environmental stressors on honeybee mortality and an additive effect on fitness (honeybee mortality, $d = 0.22$, 95% CI = 0.10 to 0.33, $n = 134$; honeybee fitness proxies, $d = -0.18$, 95% CI = −0.48 to 0.12, $n = 25$) (Extended Data Figs. 1b, 3a). For other taxa, antagonistic (*Megachile*) and additive (*Bombus* and *Osmia*) interactions were observed for mortality, but these results should be treated with caution as the sample sizes were much lower than the non-*Apis* taxa (Extended Data Fig. 3). However, given the differences in the sociality and life histories of the estimated 20,000 bee species[24], our analysis suggests that future studies are urgently required to better understand the interaction effects between environmental stressors and non-*Apis* bees. Despite this, our results confirm that exposure to multiple stressors will generally have an accumulative (additive or synergistic) negative influence on bees.

We next investigated the effects of interactions between stressors on traits that could influence bee mortality and fitness, to identify potential drivers of the main effects reported above. For example, effects on mortality may be mediated through effects on behaviour that influence the foraging efficiency of workers[25], or through effects on parasite load or immune responses[19]. However, effects of the combined exposure to stressors were antagonistic for both behaviour and parasite load (behaviour, $d = -0.22$, 95% CI = −0.42 to −0.03, $n = 76$; parasite load, $d = -0.82$, 95% CI = −1.37 to −0.27, $n = 37$) (Fig. 2b, c). In both cases, we found a high degree of heterogeneity in the data (behaviour, $I^2 = 89.4\%$; parasite load, $I^2 = 98.1\%$), and subgroup analysis suggested that this effect may be driven by particular combinations of stressor types (behaviour, agrochemical × nutrition, $d = -0.42$, 95% CI = −0.71 to −0.13, $n = 5$; parasite load, parasite × parasite, $d = -1.82$, 95% CI = −2.93 to −0.71, $n = 15$), as the effects of all other stressor combinations did not significantly depart from additive predictions. Antagonistic interactions between specific parasite types are a likely outcome if the two parasites compete for resources within the host, interacting either directly or indirectly through aspects of the host biology[26], whereas additive effects would be expected for those parasites that have qualitatively different mechanisms of action.

Although previous research has suggested that exposure to certain agrochemicals, such as neonicotinoids, may suppress the immune response of bees and leave them more vulnerable to other stressors[18,27,28], the overall effects on immune response were additive (immune response, $d = -0.21$, 95% CI = −0.55 to 0.13, $n = 32$) (Fig. 2d). Heterogeneity in the data was high ($I^2 = 92.8\%$) but subgroup analysis provided no evidence of synergistic effects when bees were exposed to multiple agrochemicals (immune response, agrochemical × agrochemical, $d = -0.38$, 95% CI = −0.80 to 0.04, $n = 13$), possibly because the agrochemicals induced a similar immune response[28]. Given that none of the interactions for behaviour, parasite load or immune response were synergistic overall, the drivers of the synergism detected for bee mortality remain unclear.

Our results show that although many classes of anthropogenic stressors may have additive effects on bee mortality and fitness proxies, exposure to combined agrochemicals can have synergistic effects that are more detrimental than would be predicted by independent risk assessments. Our meta-analysis provides a quantitative picture of broad patterns, but the high heterogeneity within our data is important from a risk assessment perspective and should not be overlooked. Synergistic interactions between non-agrochemical stressors did occur, but less frequently (Figs. 1b, 3) and were clearly more dependent on the context of the interaction (Extended Data Figs. 1, 2). Future empirical research is required to determine whether the interactions between specific stressors—such as the loss of pollen[29] or specific species of parasite (for example, deformed wing virus[30])—are more detrimental to bee health than other nutritional or pathogenic stressors. The same is true for our mechanistic response variables (for example, behaviour and parasite load). We also expect that variation may exist in the extent to which particular groups of agrochemicals interact synergistically. A recent systematic review highlighted five pesticide groups in this regard[31]; of these, two (azole fungicides and pyrethroids) featured prominently in our dataset, and when we restricted our mortality analysis to those interactions that included at least one of these groups, we found strongly synergistic effects in both cases (Extended Data Fig. 4).

Our analysis also identifies broader knowledge gaps, particularly regarding the potential effect of poor nutrition at the landscape scale; of the 356 effect sizes collected for this study only 58 concerned

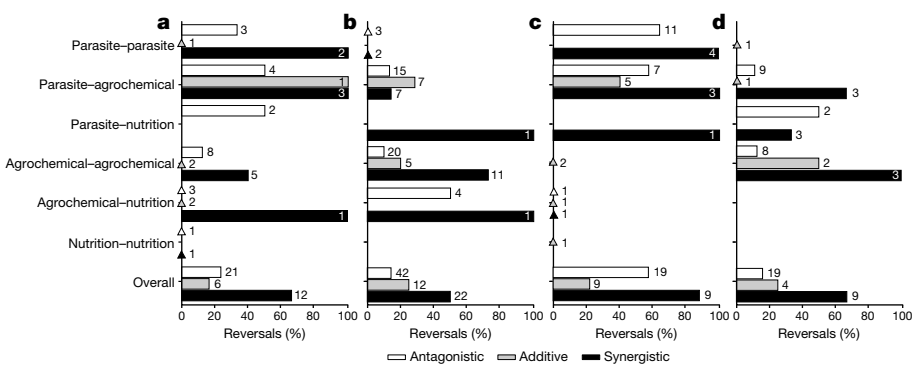

Fig. 3 | Reversal interactions. a–**d**, The percentage of additive, antagonistic and synergistic interactions between stressors that were reversal interactions for fitness proxies (**a**), behaviour (**b**), parasite load (**c**) and immune responses (**d**). The fill colour of the bars indicates the type of interaction. Triangles indicate interactions for which there were no reversals. Numbers indicate the total number of effect sizes within that category.

nutritional stressors. Given widespread habitat and flower loss[32,33], increasing intensive agriculture[10] and changes in plant phenology as a result of climate change[34], it is increasingly likely that bees will forage in environments that contain fewer floral resources. Understanding how other anthropogenic stressors interact with poor nutrition is therefore of key importance and requires further research, particularly because agri-environment schemes could be used to at least partially mitigate the consequences of poor nutrition[35]. Similarly, looking beyond parasite–nutrition–chemical interactions to other multi-stressor interactions that may affect pollinators and that occur in real landscapes (for example, including effects of climate extremes, pollution or other population-level effects) is a major challenge that is yet to be addressed.

The challenge that the non-additive effects of combined exposure poses for the agrochemical regulatory process is considerable, but our results suggest that it cannot be ignored[36–38]. Although testing all stressor combinations for all agrochemicals is not practical, it is simple to predict that certain stressors will often be present in bee populations (for example, deformed wing virus in *Apis*, *Crithidia bombi* in *Bombus* or poor nutrition in both) and thus could reasonably be included in upper tier testing. Although the patterns of combination in the use of agrochemical products represent a key knowledge gap that should be addressed to move the regulatory process forward, even here, certain combinations are predictable. For example, a requirement to perform regulatory testing that takes into account common tank mix/formulation contexts could address the concern that active ingredients may interact with the highly engineered and often toxic co-formulants and adjuvants that are applied alongside such products[39]. Ultimately, knowledge about the effects of commonly occurring combinations of agrochemicals could be critical to informing an integrated pest management approach and, potentially, to lowering the recommended dose required to treat a crop effectively[40].

Perhaps the single measure that offers the most promise for identifying commonly interacting agrochemical combinations involves a paradigm switch to include large-scale planned post-licensing observations as a final step in the regulatory process[41]. Interrogation of the results of such monitoring would offer a top-down, workable means to capture the biological complexity of such effects at scale, across multiple bee species that are not limited to *Apis*[42]. Yet post-licensing monitoring, despite being a critical feature of chemical product release for public health, is neither currently reported for agrochemicals, nor systematically carried out[41]. Ultimately, our results demonstrate that the regulatory process in its current form does not protect bees from the unwanted consequences of complex agrochemical exposure. A failure to address this and to continue to expose bees to multiple anthropogenic stressors within agriculture will result in the continued decline in bees and their pollination services, to the detriment of human and ecosystem health[12,41,43].

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-021-03787-7.

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Methods

Scope and search strategy

We used Web of Science as our search engine, using the databases 'Web of Science Core Collection' (1990 to present) and 'BIOSIS Citation Index' (2006 to present). The search terms used were based on three groups: (1) population and/or taxa (for example, bumblebee); (2) potential stressors (for example, *Varroa*); and (3) potential response variable (for example, colony fitness). The full search terms used were ("bumblebee*" OR "bumble bee*" OR "bumblebee" OR "bumble bee" OR "honey bee*" OR "honeybee*" OR "bee" OR "bees" OR "*Apis*" OR "*Bombus*" OR "solitary bee*" OR "*Osmia*") AND ("black queen cell virus" OR "BQCV" OR "acute bee paralysis virus" OR "ABPV" OR "chronic bee paralysis virus" OR "CBPV" OR "deformed wing virus" OR "DWV" OR "*Varroa destructor* virus" OR "VDV" OR "*Varroa*" OR "*Varroa*" OR "varoa" OR "Varroa mite" OR "Israeli acute paralysis virus" OR "IAPV" OR "Kashmir bee virus" OR "KBV" OR "slow bee paralysis virus" OR "SBPV" OR "sacbrood virus" OR "SBV" OR "trypanosom*" OR "*Crithidia*" OR "*Locustacarus*" OR "*Nosema*" OR "*Apicystis*" OR "gregarine" OR "nematode" OR "*Sphaerularia*" OR "parasitoid" OR "parasitoid* OR "tracheal mite" OR "tracheal mite*" OR "*Acarapis*" OR "pesticide*" OR "insecticide*" OR "neonicotinoid*" OR "parasit*" OR "nutrition" OR "pathogen*" OR "disease*" OR "virus" OR "virus*" OR "pollen" OR "nectar" OR "protein" OR "fat" OR "lipid" OR "lipids" OR "pyrethroid*" OR "herbicide" OR "herbicide*" OR "fungicide" OR "fungicide*" OR "acetamiprid" OR "clothianidin" OR "coumaphos" OR "fipronil" OR "imidacloprid" OR "thiamethoxam" OR "nutrient" OR "diet" OR "dietary") AND ("mortality" OR "survival" OR "sublethal" OR "sub-lethal" OR "sub lethal" OR "health" OR "fitness" OR "colony fitness" OR "growth" OR "reproductive output" OR "output" OR "colony output" OR "reproductive" OR "sperm" OR "reproduction" OR "queens" OR "males" OR "weight" OR "mass" OR "fecundity" OR "offspring" OR "development" OR "ovary" OR "ovary development" OR "food stores" OR "foraging" OR "navigat*" OR "homing" OR "behaviour" OR "behavior" OR "motor" OR "orientation" OR "brood care" OR "labour" OR "labor" OR "success" OR "parasite load" OR "parasite*" OR "parasite prevalence").

The literature search was initially conducted on 27 February 2018 and updated on 20 April 2020. The search yielded 14,844 papers (Extended Data Fig. 5). We excluded articles that did not include data (for example, reviews and editorials) and data from clearly irrelevant topics (for example, 'engineering aerospace' and 'nursing'), after which 12,320 papers remained and were imported from Web of Science into RefWorks ProQuest online (https://refworks.proquest.com/). We screened the titles of all papers (Extended Data Fig. 5) and excluded papers that did not mention bees or any potential environmental stressors. Each title was screened by one researcher, after an initial phase of group screening of 40 titles to ensure that screening was consistent across researchers (90% agreement between researchers). In total 10,701 titles were excluded. Abstracts were then screened to determine whether the study (1) had measured a response variable relating to bee mortality, fitness proxies, behaviour, parasite load or immune response, and (2) mentioned multiple environmental stressors (parasites, pesticides or nutritional stressors). Notably, studies were included even if the interaction between stressors was not mentioned and/or explicitly tested (this was assessed by reading the text in full, see below). During abstract screening, each abstract was read by two different researchers, and papers were only rejected when both researchers rejected the abstract—a further 2,496 papers were excluded at this stage, leaving 1,647 papers (Extended Data Fig. 5). Each of these papers were read by one researcher (C.D.M., E.J.B., H.S. or T.R.O.) to determine whether the study contained four treatment groups (control, treatment 1, treatment 2 and treatment 1 + 2, at which point a further 1,347 papers were excluded. We were unable to obtain the full text for three papers (authors were contacted) and were unable to translate the full text of one other paper, meaning that the total number of excluded papers was 1,351. We also cross-checked our search with Google Scholar by using a reduced search engine term, and checking the first 200 results (Google Scholar search terms: ("bumblebee" OR "honeybee*" OR "bee" OR "bees") AND ("parasite" OR "pathogen" OR "agrochemical" OR "pesticide" OR "insecticide" OR "nutrition") AND ("sublethal" OR "health" OR "fitness" OR "survival" OR "mortality"). This yielded zero new results, confirming that our initial search in Web of Science was reliable.

The final 296 full texts were examined for extractable data as described below (see Extended Data Fig. 5 for a PRISMA diagram).

Inclusion criteria and data extraction

For a study to be included in the meta-analysis, it had to satisfy the following inclusion criteria: (1) the paper had to consider the effect of a combination of parasites, agrochemicals or nutritional stressors on bee health; (2) the experimental design had to be fully crossed with an $n > 2$ for each treatment group[22]; and (3) means, standard deviations and sample sizes needed to be reported for each treatment group, calculable from raw data or provided by the author when contacted (see below). All studies of individual bees, caged groups or colonies at any life stage were included. Most agrochemical-based studies uncovered by our literature search investigated the effect of neonicotinoids on bees, but we included all insecticides within our analysis, including chemicals used for apiary maintenance (such as acaricides and miticides, $n = 9$). Nutritional stress was defined as one treatment group having fewer nutritional resources available to them than the other treatment group, and all bee parasites and pathogens were included within the data collected, including viruses (see Supplementary Table 5 for a full list of all stressors included in the experiment).

Many studies measured multiple response variables, which we classified into one of five categories and analysed independently of one another: (1) mortality, (2) fitness proxies, (3) behaviour, (4) parasite load and (5) immune response (see Supplementary Table 1 for list of all response variables used). In cases in which there were multiple response variables within a paper for a certain category, one response variable was randomly chosen (using the RANDBETWEEN function in Excel), except when collecting fitness proxy data, for which we would preferentially choose reproductive output (number of sexual offspring produced for cases for which gyne data were available; or otherwise the number of males produced) over other variables (Supplementary Table 1). The approach of randomly selecting a single effect size to extract within a category was taken because we had to contact authors for data in multiple instances, and this was viewed as the approach most likely to get a response. For all categories, if there were multiple time points recorded for a particular variable, the time points were chosen randomly unless otherwise stated (Supplementary Table 1). For categories other than mortality, the sample size for studies using cages of more than one bee was at the cage level, for cases in which the relevant data were reported and the n value relating to the standard deviation was clear. The number of studies for which relevant data was clearly reported at the cage level was 3 out of 8 studies using cages (fitness; total studies = 22); 9 out of 18 (behaviour; total studies = 31); 2 out of 11 (parasites; total studies = 22); 0 out of 6 (immune; total studies = 11). For mortality studies, 33 out of 64 studies used cages, but we used the number of individuals as the sample size as only three studies had the raw data to calculate the standard deviation at the cage level or reported a cage-level standard deviation. Many studies using *Apis mellifera* follow the OECD guidelines[44] when designing mortality studies and we suggest that it may be pertinent for the reporting guidelines to be updated to include data on cage level replication in the future. Most data were obtained by extracting information from the text, tables or figures using WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/) ($n = 280$) and/or raw data published alongside the paper ($n = 66$). In cases in which we could not extract all of the required information from the text, we contacted the authors and we were successful in 49 cases. Ultimately, we successfully extracted data from 100

papers (which yielded 385 effect size) between the years 1991 and 2020 (see uploaded datasets (https://osf.io/8xnua/) for all texts included and for rejected texts with reasons; and Extended Data Fig. 5 for a PRISMA diagram). In addition, 29 effect sizes were removed at the analysis stage (see below), which resulted in a total of 356 effect sizes from 90 papers (Extended Data Fig. 5).

Statistical analysis

All analyses were conducted in R (v.3.5.2), using the package metafor (v.2.1-0)[45]. Each category of response variables (mortality, fitness, behaviour, parasite load and immunity) was analysed separately.

To estimate each interaction effect size, we first calculated the additive predicted value for the two stressors based on the sum of their single independent effects: ((mean stress 1 − mean control) + (mean stress 2 − mean control) + mean control). At this stage, as previously described[22], we removed effect sizes when the additive predicted value was impossible (for example, mortality > 100%), because in such cases the true interaction effect cannot be estimated. For example, if hypothetical stressors A and B both cause 60% mortality relative to the control group, the predicted mortality of the combined treatment exceeds the boundary of observable values (100%), rendering synergistic and additive interactions impossible to detect, and apparently antagonistic interactions unreliable. This resulted in the removal of 29 effect sizes from 10 studies. For the remaining 356 data points, the interaction effect size was then calculated as a standardized mean difference (Hedges' *d*) by comparing the predicted additive effect to the actual observed effect when bees were exposed to both stressors in combination[22] (Supplementary Information).

In cases in which independent effects of both stressors were negative, we inverted the sign of the interaction effect such that a positive Hedges' *d* indicated synergism and a negative effect indicated antagonism. Hence, for all categories, a Hedges' *d* value close to zero depicts an additive interaction, whereby the sum of the combined interaction effect is not significantly different from that predicted by the individual stressors. In cases in which the independent effects of two stressors had opposing directional effects (one positive and one negative), these were recorded as reversal interactions and, if the sign of the largest of the two effects was negative, we inverted the sign of the final calculated interaction effect[22]. Therefore, reversal interactions could be antagonistic, additive or synergistic (Figs. 1b, 3).

For all datasets, we used a random-effects model (rma), with a restricted maximum-likelihood estimator (REML) to determine the overall grand mean (Hedges' *d*) with 'source paper' included within each model as a random factor to control for the non-independence of multiple effect sizes from the same studies. To explain the between-study heterogeneity in effects and to test whether interaction effects differ depending on the combination of stressors applied, we conducted a meta-regression with stressor pairing included as a fixed factor and paper included as a random factor. Subgroup analysis was used to investigate the effects of specific combinations of stressors (for example, agrochemicals and parasites, nutrition and parasites, and so on) and the significance of the interaction effects was determined using 95% CIs, which were calculated around the mean effect. The 95% CIs that do not cross the zero line indicate significant synergistic (positive values) or antagonistic (negative values) interactions (in cases in which $n = 1$, Hedges' *d* and the 95% CI represent the output from the singly calculated effect size).

To test and adjust for a possible publication bias, a trim-and-fill technique was used on all variables measured[46]. The results did not change across the mortality, parasite-load and immune-response data (mortality, $d = 0.19$, 95% CI = 0.08 to 0.29; parasite load, $d = -0.81$, 95% CI = −1.36 to −0.26; immune response, $d = -0.20$, 95% CI = −0.54 to 0.31) and only changed marginally for the fitness proxy and behaviour data (fitness proxies, $d = 0.24$, 95% CI = −0.02 to 0.05; behaviour, $d = 0.07$, 95% CI = −0.13 to 0.28). Notably, this bias was towards studies with antagonist results, which suggests that the observed results on behaviour and fitness may underestimate the interaction effects between stressors (Extended Data Fig. 6). Observation of the funnel plots also identified two outliers, one each in the mortality and immune data. Cook's distance was less than one[47], so we retained them within the analysis; however, as a sensitivity analysis, we re-ran the analysis without them and the results did not change for the mortality data and changed marginally—from additive to antagonistic—for the immune data (mortality, $d = 0.17$, 95% CI = 0.07 to 0.27; immune, $d = -0.31$, 95% CI = −0.56 to −0.07). To examine the robustness of our results to the non-independence of data from studies with caged bees (see above) we ran a sensitivity analysis for bee mortality because this dataset relied most heavily on data using individual-level *n* values and therefore would be most likely to be affected by the non-independence of data points. We calculated the effective sample size for caged studies and found no qualitative differences between the results of the analyses conducted using the number of individuals or effective sample size (see Supplementary Information for detailed methods and results), supporting the robustness of our analysis above.

The majority of the data gathered considered the interaction effects of stressors on honeybees rather than on wild bees. To assess whether results differed across taxa, we analysed both the full dataset (in which *Apis* and non-*Apis* bees were included) and subset datasets according to genus (Extended Data Fig. 3). We conducted the same analysis as described above across both datasets and found qualitatively similar results in both cases.

We were also interested in determining whether the field realism of agrochemical exposure influenced the interaction effects between stressors. The definition of field realism is highly contentious, as application rates vary across countries with different mitigation measures and legislation. We based field realism on reported residue concentrations in treated crops and—as in previous research[48]—re-classified the field realism of agrochemical exposure for each of the effect sizes generated in this meta-analysis. Both acute and chronic exposure regimes were included within the data gathered. Acute exposure occurs when a foraging bee feeds and/or comes into contact with an agrochemical and receives a single dose of the toxin. Chronic exposure occurs when a bee is repeatedly exposed to agrochemicals over a sustained period of time (for example, during mass flowering of a treated crop, such as oilseed rape). For orally exposed bees, field realism of chronic exposure was based on the average concentration (ppb) of agrochemical residue found in the nectar and pollen of treated crops (Supplementary Table 2). For acute oral exposure the concentration was combined with the mean amount of nectar collected by foraging bees (Supplementary Table 3). For contact toxicity tests, we considered the mean reported concentration of active substance within the tank of spray solutions (Supplementary Table 4). Any values above these dosages were considered above field-realistic. In cases in which multiple agrochemicals were used, the results were coded as above field-realistic when at least one agrochemical exposed was above the estimated field-realistic levels. When residue data were not available, the corresponding effect sizes were not included in the analysis. We used the same approach as described above to estimate the effect sizes and 95% CIs.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this paper.

Data availability

All data used in this analysis are available at OSF (https://osf.io/8xnua/).

Code availability

All code used in this analysis is available at OSF (https://osf.io/8xnua/).

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Author contributions H.S., E.J.B., C.D.M., T.R.O. and M.J.F.B. conceived the idea for the study in a discussion group. H.S. and E.B. oversaw and managed the data collection. H.S., E.B., C.D.M. and T.R.O. carried out the literature search and collected the data. H.S. and E.L. conducted the statistical analysis and H.S. wrote the first version of the manuscript. H.S., E.J.B., J.K., E.L. and M.J.F.B. contributed to the writing of subsequent drafts.

Competing interests The authors declare no competing interests.

Additional information
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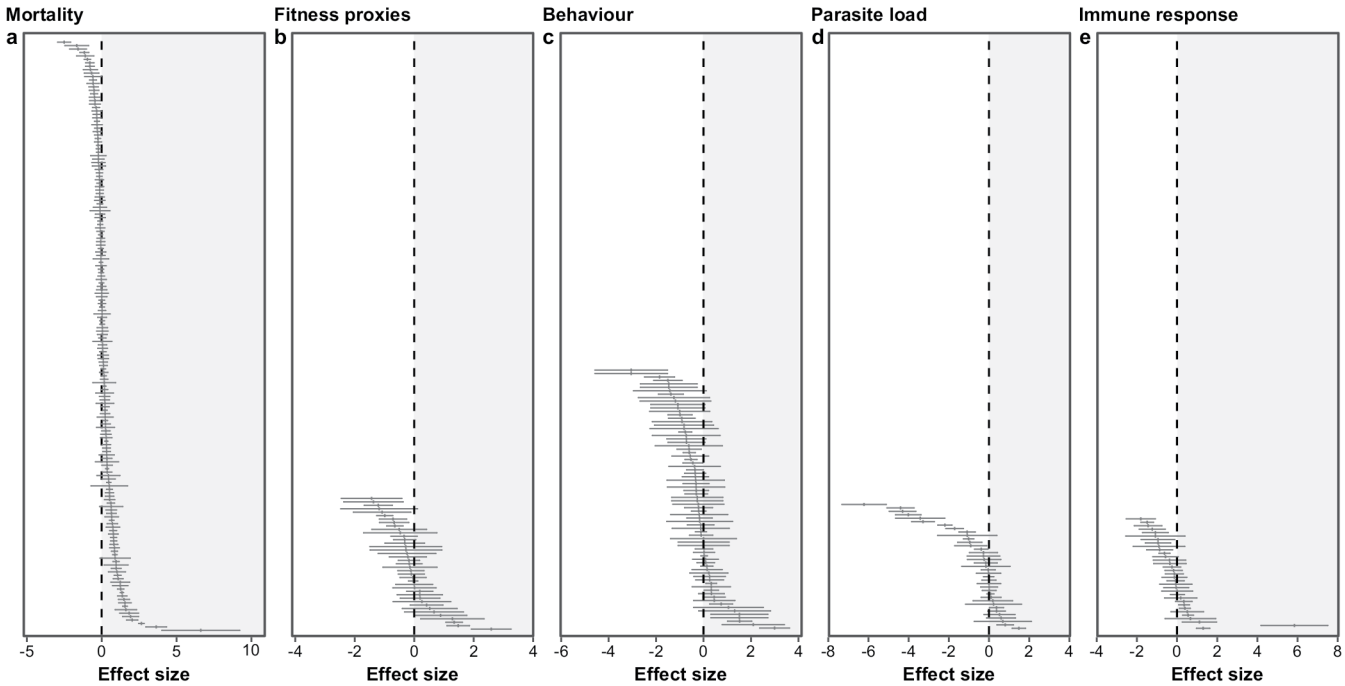
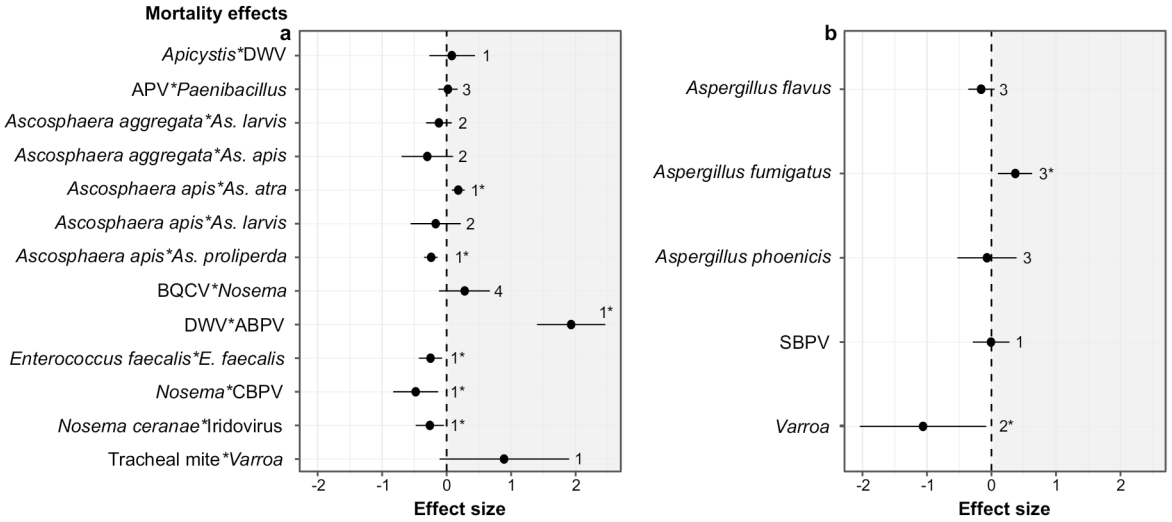
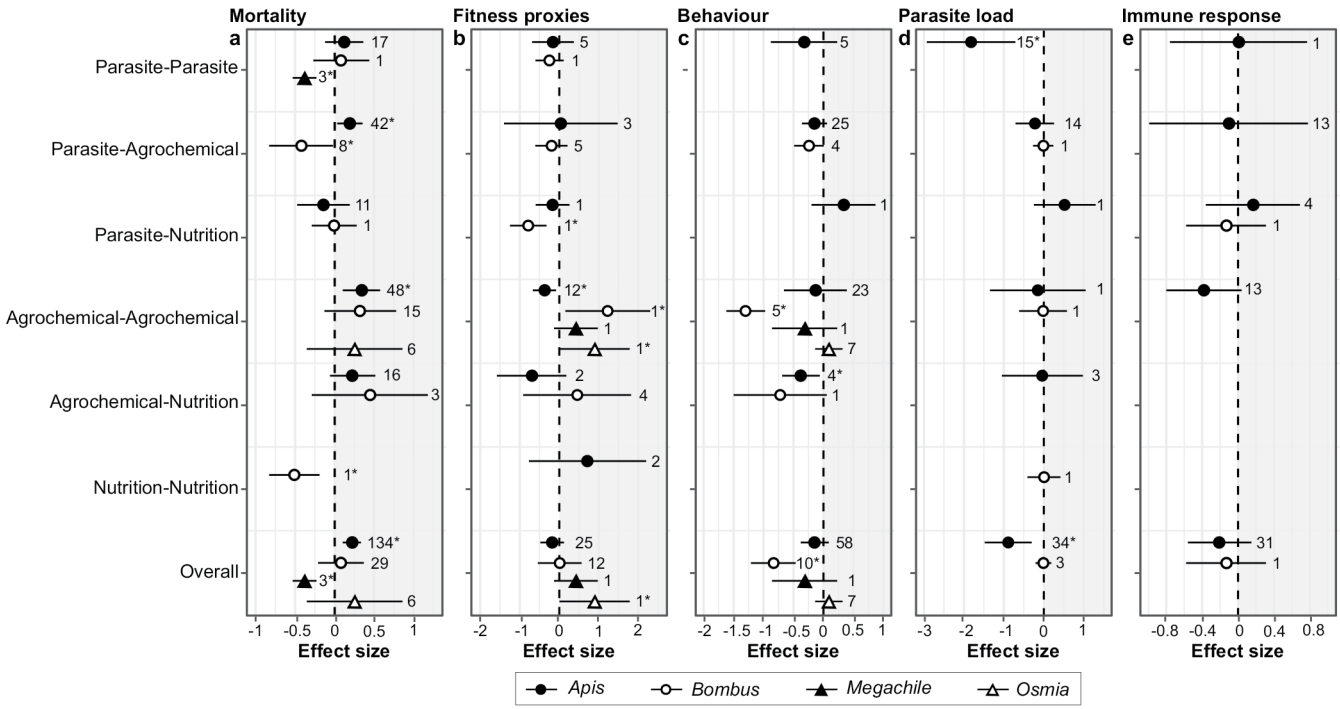


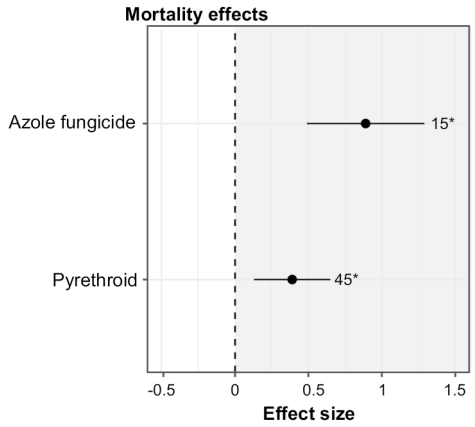
Extended Data Fig. 1 | Distribution of Hedges' *d* values for the individual effect sizes included for the interaction effects of parasites, agrochemicals and nutritional stressors for bee response variables. a–**e**, Distributions are shown for mortality (**a**), behaviour (**b**), fitness (**c**), parasite load (**d**) and immune responses (**e**). Data are shown as Hedges' *d* values ± 95% CI. Effect sizes are sorted for each response variable from most negative to most positive. Each mean ± 95% CI represents a different data point, hence there are more effect sizes than number of studies. Interactions are synergistic when the effect size is positive and the 95% CI does not include zero, antagonistic when the effect size is negative and the 95% CI does not include zero and additive when the 95% CI includes zero. Note that each panel is presented on a different scale.



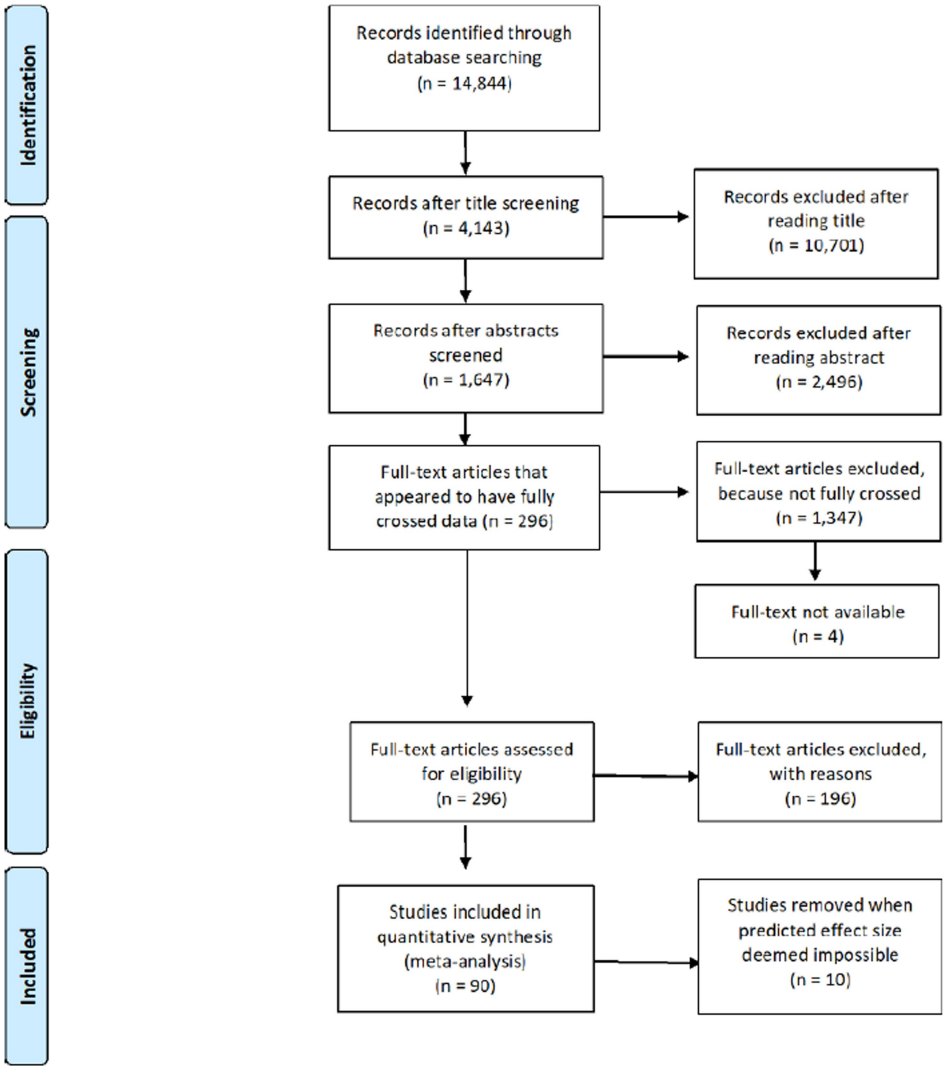
Extended Data Fig. 2 | Hedges' *d* values for interactions between specific stressors on bee mortality. a, Interactions between combinations of parasite stressors. **b**, Interactions between combinations of parasite and nutritional stressors. Data are shown as Hedges' *d* values ± 95% CI. The interactions are synergistic when the effect size is positive and the 95% CI does not include zero, antagonistic when the effect size is negative and the 95% CI does not include zero and additive when the 95% CI includes zero. Numbers next to the 95% CIs indicate the number of effect sizes in each category. Asterisks indicate that the 95% CI does not include zero.



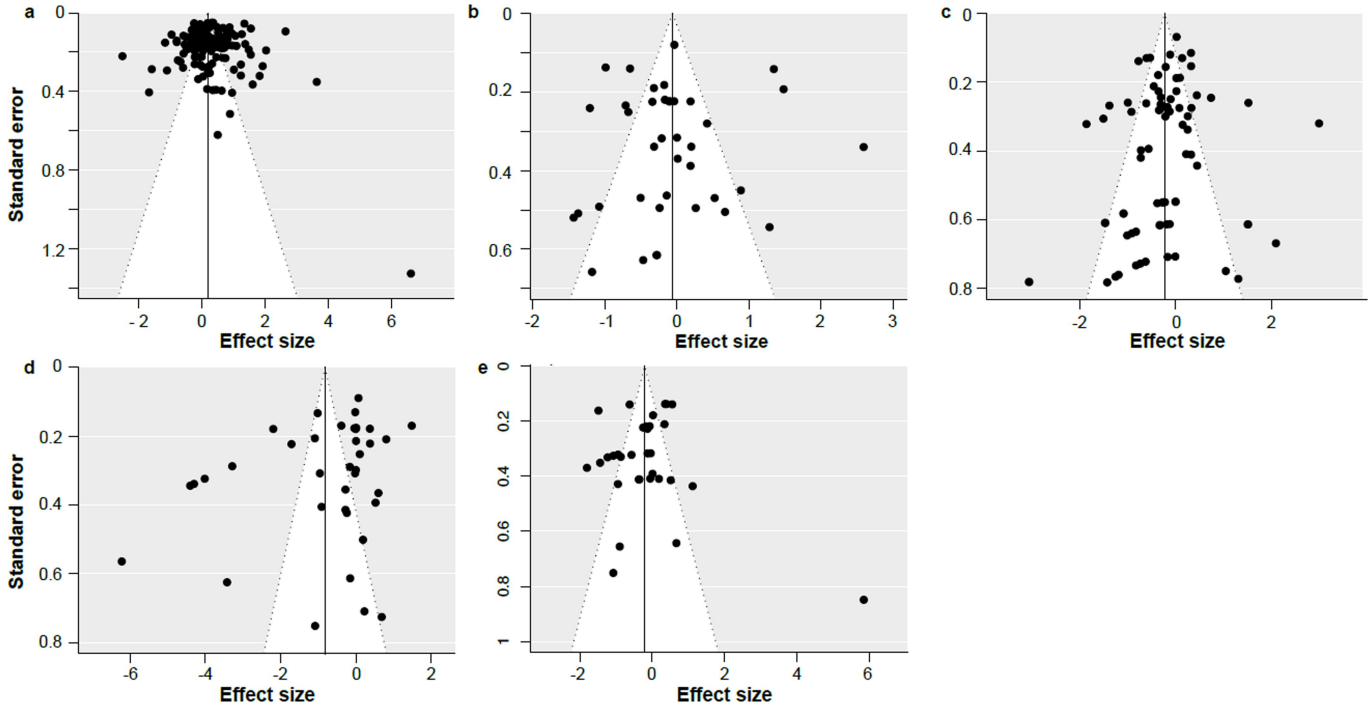
Extended Data Fig. 3 | Hedges' *d* values for different bee genera. a–**e**, Data are shown as Hedges' *d* values ± 95% CI for mortality (**a**), behaviour (**b**), fitness proxies (**c**), parasite load (**d**) and immune responses (**e**). The genus is indicated by the colour and shape of the symbol. Interactions are synergistic when the effect size is positive and the 95% CI does not include zero, antagonistic when the effect size is negative and the 95% CI does not include zero, and additive when the 95% CI includes zero. Numbers next to the 95% CIs indicate the number of effect sizes in each category. Asterisks indicate that the 95% CI does not include zero. Note that each panel is presented on a different scale.



Extended Data Fig. 4 | The interaction effects of different agrochemical classes on bee mortality response measures. Hedges' *d* values ± 95% CI are shown. Asterisks indicate that the 95% CI does not include zero. Numbers next to the 95% CIs indicate the number of effect sizes in each category. Note that effect sizes for azole fungicide × pyrethroid are included in both groups.



Extended Data Fig. 5 | Modified PRISMA flowchart. A flowchart depicting the number of studies included or excluded at each stage of the literature search.



Extended Data Fig. 6 | Funnel plots of the full models of the interactions between specific stressors. a–**e**, Plots represent the models for mortality (**a**), behaviour (**b**), fitness proxies (**c**), parasite load (**d**) and immune responses (**e**).

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Corresponding author(s): Harry Siviter

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Reporting Summary

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☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
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☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/) was used to extract data from figures when raw data was not available.
Data analysis	R (version 3.5.2) was used for the analysis with the package metafor (version 2.1-0)

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
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The datasets generated during the current study are available at https://osf.io/8xnua/

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Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	The study was a meta-analysis that looked at the interactions between agrochemicals, parasites and nutritional stress on bee health.
Research sample	We collected data from 90 papers, that produced 356 effect sizes across 5 different data categories (bee survival, fitness proxies, bee behaviour, parasite load and immune response).
Sampling strategy	We conducted a systematic literature search and extracted all available data.
Data collection	Data was collected by HS, EB, CM & TO.
Timing and spatial scale	NA- This is a meta-analysis based study.
Data exclusions	Data was not included when we could not extract it from published manuscripts. In cases when this occurred authors were contacted.
Reproducibility	This is a meta-analysis based study. Code and data provided.
Randomization	NA- This is a meta-analysis based study.
Blinding	NA- This is a meta-analysis based study. It was not possible to extract data from the literature blind.

Did the study involve field work? ☐ Yes ☒ No

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging