



UNIVERSITÉ  
DE NAMUR

# Institutional Repository - Research Portal

# Dépôt Institutionnel - Portail de la Recherche

researchportal.unamur.be

## RESEARCH OUTPUTS / RÉSULTATS DE RECHERCHE

### Towards a unified study of multiple stressors

Orr, James A.; Vinebrooke, Rolf D.; Jackson, Michelle C.; Kroeker, Kristy J.; Kordas, Rebecca L; Mantyka-Pringle, Chrystal; Van den Brink, Paul J.; De Laender, Frederik; Stoks, Robby; Holmstrup, Martin; Matthaei, Christoph D.; Monk, Wendy A.; Penk, Marcin R.; Leuzinger, Sebastian; Schäfer, Ralf B.; Piggott, Jeremy J.

*Published in:*  
Proceedings of the Royal Society B: Biological Sciences

*DOI:*  
[10.1098/rspb.2020.0421](https://doi.org/10.1098/rspb.2020.0421)

*Publication date:*  
2020

*Document Version*  
Peer reviewed version

[Link to publication](#)

*Citation for published version (HARVARD):*  
Orr, JA, Vinebrooke, RD, Jackson, MC, Kroeker, KJ, Kordas, RL, Mantyka-Pringle, C, Van den Brink, PJ, De Laender, F, Stoks, R, Holmstrup, M, Matthaei, CD, Monk, WA, Penk, MR, Leuzinger, S, Schäfer, RB & Piggott, JJ 2020, 'Towards a unified study of multiple stressors: divisions and common goals across research disciplines', *Proceedings of the Royal Society B: Biological Sciences*, vol. 287, no. 1926, 20200421.  
<https://doi.org/10.1098/rspb.2020.0421>

### General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

1   **Title:** Towards a Unified Study of Multiple Stressors: Divisions and Common Goals Across  
2   Research Disciplines

3

4   **Authors:** James A. Orr<sup>1</sup>, Rolf D. Vinebrooke<sup>2</sup>, Michelle C. Jackson<sup>3</sup>, Kristy J. Kroeker<sup>4</sup>,  
5   Rebecca L. Kordass<sup>5</sup>, Chrystal Mantyka-Pringle<sup>6,7</sup>, Paul J. Van den Brink<sup>8,9</sup>, Frederik De  
6   Laender<sup>10</sup>, Robby Stoks<sup>11</sup>, Martin Holmstrup<sup>12</sup>, Christoph D. Matthaei<sup>13</sup>, Wendy A. Monk<sup>14</sup>,  
7   Marcin R. Penk<sup>1</sup>, Sebastian Leuzinger<sup>15</sup>, Ralf B. Schäfer<sup>16</sup>, Jeremy J. Piggott<sup>1</sup>

8

9

10   **Institutional Affiliations:**

- 11       1. School of Natural Sciences, Trinity College Dublin, The University of Dublin, Dublin,  
12           Ireland
- 13       2. Department of Biological Sciences, University of Alberta, Edmonton, Alberta, Canada
- 14       3. Department of Zoology, University of Oxford, Oxford, UK
- 15       4. Ecology and Evolutionary Biology, University of California Santa Cruz, Santa Cruz,  
16           California, USA
- 17       5. Department of Life Sciences, Imperial College London, Silwood Park Campus,  
18           Berkshire, UK
- 19       6. School of Environment and Sustainability, University of Saskatchewan, Saskatoon,  
20           Saskatchewan, Canada
- 21       7. Wildlife Conservation Society Canada, Whitehorse, YT, Canada
- 22       8. Aquatic Ecology and Water Quality Management Group, Wageningen University,  
23           P.O. Box 47, 6700 AA Wageningen, The Netherlands
- 24       9. Wageningen Environmental Research, P.O. Box 47, 6700 AA Wageningen, The  
25           Netherlands

26        10. Research Unit of Environmental and Evolutionary Biology, Namur Institute of  
27              Complex Systems, and Institute of Life, Earth, and the Environment, University of  
28              Namur, Rue de Bruxelles 61, 5000 Namur, Belgium  
29        11. Evolutionary Stress Ecology and Ecotoxicology, University of Leuven, Leuven,  
30              Belgium  
31        12. Department of Bioscience, Aarhus University, Silkeborg, Denmark  
32        13. Department of Zoology, University of Otago, Dunedin, New Zealand  
33        14. Environment and Climate Change Canada at Canadian Rivers Institute,  
34              Faculty of Forestry and Environmental Management, University of New Brunswick,  
35              Fredericton, New Brunswick, Canada.  
36        15. Institute for Applied Ecology, Auckland University of Technology, Auckland, New  
37              Zealand  
38        16. Quantitative Landscape Ecology, iES - Institute for Environmental Sciences,  
39              University Koblenz-Landau, Landau in der Pfalz, Germany  
40

41        **Keywords:** Multiple Stressors, Global Change Factors, Multiple Drivers, Synergism,  
42              Antagonism, Combined Effects  
43  
44  
45  
46  
47  
48  
49  
50

51   **Abstract:**

52   Anthropogenic environmental changes, or ‘stressors’, increasingly threaten biodiversity and  
53   ecosystem functioning worldwide. Multiple-stressor research is a rapidly expanding field of  
54   science that seeks to understand and ultimately predict the interactions between stressors.  
55   Reviews and meta-analyses of the primary scientific literature have largely been specific to  
56   either freshwater, marine or terrestrial ecology, or ecotoxicology. In this cross-disciplinary  
57   study, we review the state of knowledge within and among these disciplines to highlight  
58   commonality and division in multiple-stressor research. Our review goes beyond a description  
59   of previous research by using quantitative bibliometric analysis to identify the division  
60   between disciplines and link previously disconnected research communities. Towards a  
61   unified research framework, we discuss the shared goal of increased realism through both  
62   ecological and temporal complexity, with the overarching aim of improving predictive power.  
63   In a rapidly changing world, advancing our understanding of the cumulative ecological  
64   impacts of multiple stressors is critical for biodiversity conservation and ecosystem  
65   management. Identifying and overcoming the barriers to interdisciplinary knowledge  
66   exchange is necessary in rising to this challenge. Division between ecosystem types and  
67   disciplines is largely a human creation. Species and stressors cross these borders and so  
68   should the scientists who study them.

69

70

71

72

73

74

75

76 **1. Introduction**

77 The most severe threats to global biodiversity and ecosystem functioning are anthropogenic  
78 environmental changes, or “stressors,” such as habitat loss, climate change, pollution and  
79 invasive species (1, 2). These stressors often interact in complex and unexpected ways (3-6).  
80 Multiple-stressor research seeks to understand and predict interactions between stressors.  
81 Importantly, due to these interactions the combined effect of two or more stressors is  
82 frequently more than (synergistic) or less than (antagonistic) expected based on their  
83 individual effects (7, 8). The study of multiple stressors is not a novel pursuit in science;  
84 toxicologists, and later ecotoxicologists, have been identifying the combined impact of  
85 multiple chemical stressors on individual organisms or populations for almost a century (9,  
86 10). Multiple-stressor research has now expanded to more diverse stressor combinations and  
87 has become a prominent feature of global change biology. Consequently, the concepts and  
88 terms used in the multiple-stressor literature have become common in mainstream biology.

89

90 Aquatic, terrestrial, and ecotoxicological investigations into multiple stressors differ greatly in  
91 their approach. In the freshwater and marine ecology literature, numerous studies have  
92 measured biological responses to specific stressor combinations (3, 5). Such work has been  
93 conducted across the globe, from the Arctic (11) to the Antarctic (12), and has focused on  
94 virtually all taxonomic groups, including bacteria (13), algae (14), invertebrates (15),  
95 amphibians (16), and fish (17). Parallel to this research, and with almost no lateral exchange,  
96 the effects of multiple stressors on ecosystems have been the focus of many terrestrial  
97 experiments (18-20). Contrary to the freshwater and marine literature, the response variables  
98 of interest in terrestrial studies are mostly the fluxes and pools of matter such as water,  
99 carbon, nitrogen or other nutrients. Another discipline that has dealt with impacts of multiple  
100 stressors is ecotoxicology, which focuses on the effects of chemical pollutants and their

101 interactions with other stressors (6, 21, 22). Although freshwater, marine and terrestrial  
102 subdisciplines exist within ecotoxicology, they share a basic scientific foundation (e.g.  
103 methods, journals and conferences), which merits their aggregation as one discipline in this  
104 review.

105

106 Regardless of differing approaches, the underpinning concepts of multiple-stressor research  
107 are similar across the different disciplines. Despite this, exchange and cross-fertilization of  
108 ideas and conceptual models has been limited. For example, the co-tolerance concept (23), a  
109 number of stressor interaction classification systems (e.g., 7), and various null models  
110 predicting the combined effect of stressors (e.g., 24, 25) have virtually escaped the terrestrial  
111 ecology community (4, 18, 26). Moreover, models and methods developed in the context of  
112 ecotoxicology have largely been ignored in aquatic and terrestrial ecology (27). Even reviews  
113 and meta-analyses of the multiple-stressor literature have primarily been specific to either  
114 freshwater (5), marine (3) or terrestrial systems (18), or to ecotoxicology (6) (but see: 28, 29).

115

116 Differences in terminology attest to the disconnection of freshwater, marine and terrestrial  
117 ecologists, as well as ecotoxicologists, from each other. For example, while the terms  
118 “stressors”, “antagonism” and “synergism” are common within the freshwater, marine and  
119 ecotoxicology literature (5, 24, 30), many terrestrial and some marine ecologists often use the  
120 terms “drivers/factors”, “dampening” and “amplification”, respectively (18, 26, 31, 32). Other  
121 terms such as “cumulative effects”, “combined effects”, “net effects” or “interactive effects”  
122 are used across all disciplines, but without consistent definitions (3, 33, 34). The pre-existing  
123 separation among scientific disciplines further contributes to this division in multiple-stressor  
124 research, exemplified by how ecologists tend not to cite work carried out in systems different  
125 from their own (35, 36).

126

127 A better exchange between the different disciplines studying multiple stressors would be  
128 highly desirable. The separation of disciplines, including inconsistency in the terminology,  
129 hampers progress in multiple-stressor research because scarce resources are wasted due to the  
130 parallel development of similar methods and tools in different disciplines. Equally,  
131 incomplete literature searches and meta-analyses create an ignorance of the complete  
132 evidence, which can mislead research directions, impede the spread of ideas and slow down  
133 development of overarching theoretical concepts. In this cross-disciplinary review we use  
134 quantitative bibliometric analysis to identify and illustrate the division between multiple-  
135 stressor researchers from different disciplines, we discuss qualitative differences in methods and  
136 terminology between the disciplines, and we provide a common glossary to harmonise concepts  
137 and terminology. Subsequently, we identify and discuss three common research goals that all  
138 multiple-stressor researchers share towards a unified research framework, specifically: (i)  
139 increased ecological complexity, (ii) increased temporal scale and realism, with the overarching  
140 aim of (iii) improving predictive power.

141

142

## 143 **2. Bibliometric Analysis**

### 144 **2.1 Methods**

145 Using terms identified during our cross-discipline review we performed a search of the *ISI*  
146 *Web of Knowledge* database (<https://apps.webofknowledge.com>) to collect publications from  
147 the multiple-stressor literature (SM1). Next, we constructed citation networks where nodes  
148 represent specific publications and links indicate a citation between connected publications.  
149 Clustering algorithms and citation analysis were used to group publications that cite each  
150 other more than they cite other publications in the same network (37). To enhance visibility,

151 only the most influential publications (top 300 most cited) were used to construct the citation  
152 networks. Given that this was biased towards marine and freshwater publications, the 25 next  
153 most highly cited terrestrial and ecotoxicological publications were added to ensure a similar  
154 number of publications across disciplines. The largest connected network (150 publications:  
155 SM2) from this pool of 350 publications was selected, ignoring publications outside the  
156 multiple-stressor literature. We also created term networks, based on the 150 multiple-stressor  
157 publications, using text-mining techniques to identify different clusters of terminology. The  
158 publications and terms were manually assigned to one of the disciplines. For details on the  
159 bibliometric analysis, see SM2.

160

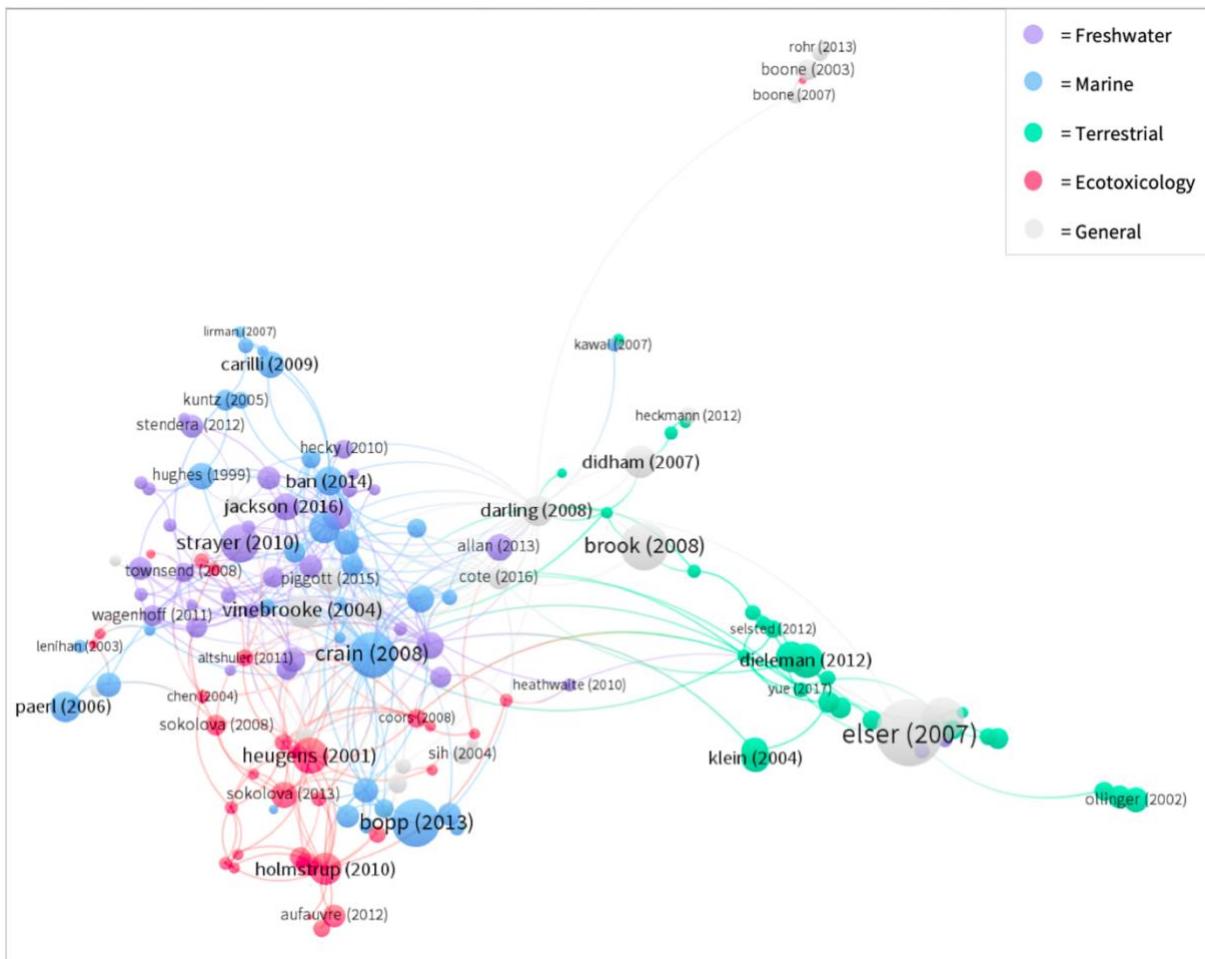
## 161 **2.2 Results**

162 A citation network of 150 publications from the multiple-stressor literature with colours  
163 representing clusters emerged from our analysis (SM3). The size of the nodes was based on  
164 the number of citations normalized by age of publication. When the size of the nodes was  
165 based on the number of links in the network, emphasis was put on different nodes (SM4).  
166 Supplementing our networks with additional publications reduced a bias in terms of nodes but  
167 may not have reduced a bias in terms of links (citations); on average the freshwater and marine  
168 publications had more citations than publications from the other disciplines. Consequently, we  
169 constructed larger networks using a lower common threshold of citations resulting in networks  
170 based on the 500, 1000, 1500 and 2000 most highly cited publications (SM5). Although these  
171 larger networks are much more difficult to read, clustering patterns similar to SM3 are  
172 conserved.

173

174

175



176

177 **Figure 1:** Citation network where the nodes represent publications and the links indicate the  
 178 presence of a citation between connected publications. The size of the nodes represents the  
 179 number of citations normalized by age. The distance between nodes is calculated using a  
 180 citation analysis algorithm which determines the relatedness of items based on the number of  
 181 times they cite each other. The colours of the nodes and their links represent the disciplines  
 182 they belong to.

183

184 Customizing the colours of the nodes and links to represent the different disciplines reveals  
 185 the division between disciplines (Figure 1). Some of the key papers in the multiple-stressor  
 186 literature are cited across disciplines and are found towards the center of the networks (7, 8,  
 187 23, 28, 29). Although the freshwater, marine and ecotoxicology literature clearly have their  
 188 own clusters, these disciplines substantially overlap (particularly freshwater and marine). In

189 contrast, the terrestrial publications form a distinct cluster that is only connected to the rest of  
190 the network via five key nodes, which are mostly meta-analyses or reviews (18, 28, 29, 34,  
191 38).

192

193 A heat map was produced to quantify the division between disciplines in the citation networks  
194 (SM6). The terrestrial publications are found almost exclusively in cluster 1 (82.8%) of the  
195 citation network (SM3). The ecotoxicological publications are found primarily in cluster 4  
196 (54.8%). The freshwater publications are found primarily in clusters 2 (44.1%) and 6 (23.5%).  
197 The marine publications are well represented in all clusters in the network except for clusters  
198 1 and 4.

199

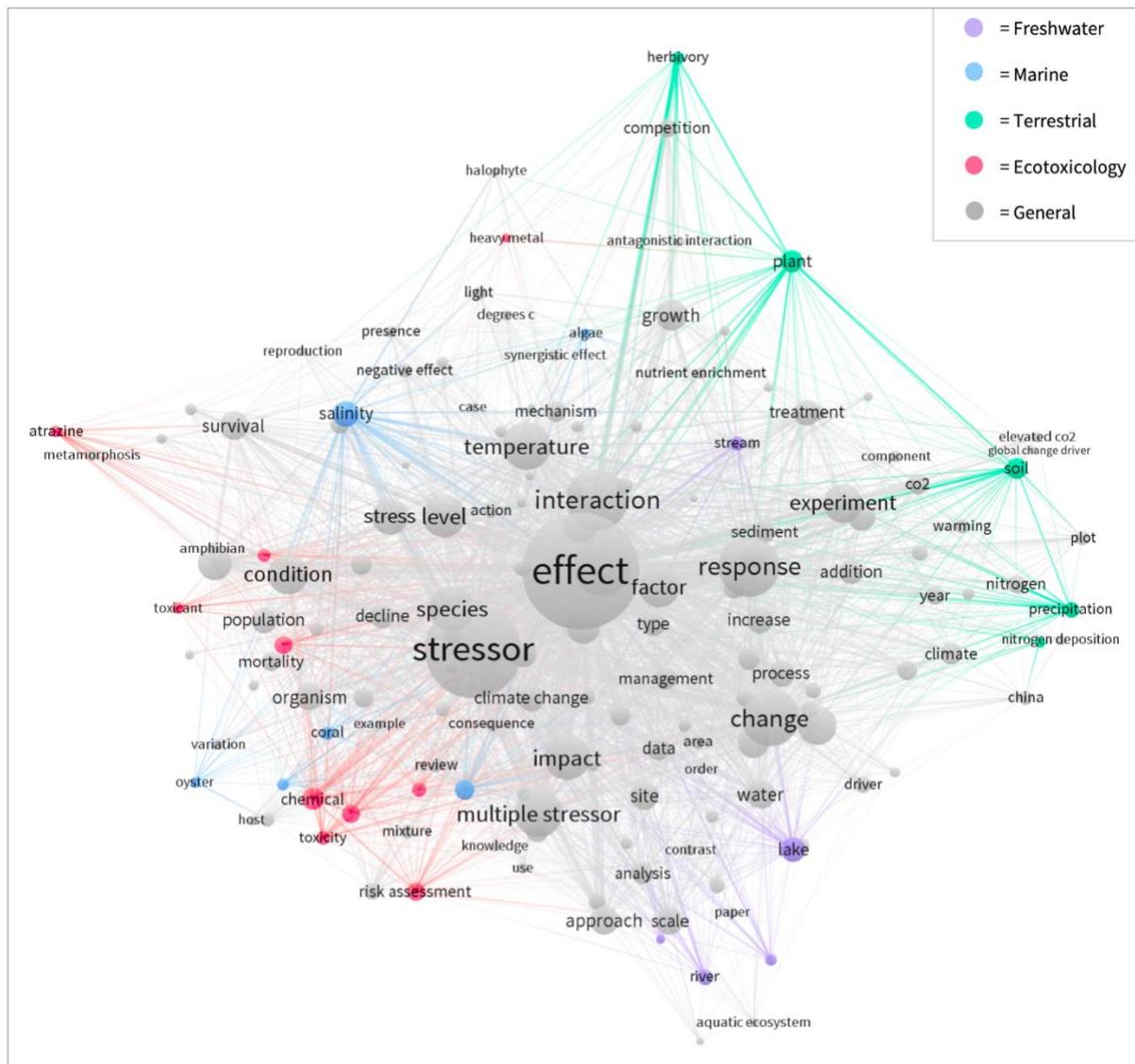
200 In the term network, nodes towards the center of the network (e.g. effect, interaction,  
201 response) are used by all multiple-stressor researchers, whereas some nodes at the edges of  
202 the network are discipline-specific (Figure 2). The coloured nodes have been assigned to  
203 specific disciplines to outline the approximate location of disciplines in the network (full list  
204 of terms in SM7). These coloured terms act as markers against which the location of general  
205 terms of interest can be compared. For example, the term “multiple stressor” is found towards  
206 the edge of the network near freshwater, marine and ecotoxicological terms; it is on the  
207 opposite side of the network from where the terrestrial terms are. Similarly, the term “global  
208 change driver” is found among the terrestrial terms and away from the terms specific to the  
209 other disciplines.

210

211

212

213



214

215 **Figure 2:** Term network constructed using text-mining techniques with the publications from  
 216 the citation networks (Figure 1) as source documents. Terms that occurred at least 10 times  
 217 were included. The size of the nodes represents the frequency of a term and the links  
 218 represent co-occurrence. The colours of the nodes and their links represent the disciplines  
 219 they are associated with.

220

221

222

223

224 **3. Synthesis**

225 As well as bibliometric analysis, a review of the literature was carried out to investigate how  
226 disciplines differ in their study of multiple stressors (summarized in SM8). Our aim was to  
227 compare the predictor and response variables, methods and key findings from meta-analyses  
228 of multiple-stressor research across disciplines. One of the key findings from our review was  
229 that multiple-stressor researchers from different disciplines, despite studying fundamentally  
230 the same phenomena, are using different terminology for predictor variables and interactions.  
231 Equally, the most common predictor and response variables studied differ among disciplines  
232 (Table 1), which likely reflects alternative perspectives on which stressors are most important  
233 (36).

234

235 Another difference between and within disciplines is how researchers define a stressor. Many  
236 researchers associate stress with a negative biological response (23, 39) but others argue that  
237 the effect of any stressor is context dependent and can be positive or negative (7, 29, 40). For  
238 example, all common stressors (predictor variables) listed in Table 1 can cause positive or  
239 negative effects depending on the study species or the response variable. Another element to  
240 consider is whether a stressor can be natural, or only anthropogenic. Some researchers keep  
241 the definition as broad as possible (29, 41) whereas others state that what separates a stressor  
242 from a “driver”, “factor” or “disturbance” is that it is anthropogenic (7, 42). For the latter  
243 definition, it is important to note that natural factors such as predation or herbivory can  
244 become stressors under human modification.

245

246

247

248 **Table 1:** Comparison of multiple-stressor research across freshwater, marine and terrestrial  
 249 ecology and ecotoxicology.

Discipline	Terminology for predictor variables	Terminology for interactions	Common predictor variables	Common response variables	Key references
<b>Freshwater</b>	Stressor	Additive Synergistic Antagonistic Reversal	Increased temperature Altered flow Nutrients Toxicants Habitat modification Invasive species	Population metrics Functional traits Biodiversity	(5, 43, 44)
<b>Marine</b>	Stressor Driver	Additive Synergistic Antagonistic	Increased temperature Acidification Pollutants Nutrients High/low salinity Hypoxia Habitat modification	Physiology Population metrics Functional traits Biodiversity	(3, 30, 45)
<b>Terrestrial</b>	Factor Driver	Additive Synergistic Antagonistic Dampening Amplifying Counteracting	Increased temperature Increased CO <sub>2</sub> Land use change Nutrient modification Altered precipitation Invasive species	Fluxes and pools of elements, compounds and nutrients Productivity Biodiversity	(18, 34, 46)
<b>Ecotoxicology</b>	Stressor Toxicant Toxic chemical	Additive Synergistic Antagonistic	Toxicants Increased temperature Salinization Drought Pathogens or predators	Physiology Population metrics Biodiversity	(6, 22, 24)

250

251

252 There is a clear division between terrestrial researchers, who tend not to use the term  
 253 “stressor”, and the rest of the multiple-stressor community. Terrestrial ecology has provided  
 254 crucial evidence of the combined effect of stressors, but the language used leads to multiple-  
 255 stressor meta-analyses missing these studies. That is because rather than using the common

256 terminology of multiple-stressor research (e.g., stressor, antagonism or synergism), some  
257 studies only refer to the specific factors examined and describe effects as “dampening”,  
258 “amplifying” or “counteracting forces” (26, 46, 47). For example, in Darling and Côté’s (28)  
259 meta-analysis of factorial experiments examining the effects of multiple stressors on animal  
260 mortality in freshwater, marine and terrestrial communities the keywords used in their search  
261 included “synergy”, “antagonism” and “stress” but lacked “amplifying”, “dampening” or  
262 “factor/driver”. Potentially as a result of this, only four of the 112 experiments in the meta-  
263 analysis were conducted with terrestrial organisms (excluding amphibians) (28). Hence, meta-  
264 analyses are useful in that they can identify knowledge gaps and pose new questions, but they  
265 reinforce division between disciplines when restricted to certain search terms. Another  
266 potential issue is that the same word can have different meanings or connotations in different  
267 disciplines, although this is difficult to quantify. For example, the word “stressor” is often  
268 associated with negative effects, whereas some researchers, particularly from aquatic  
269 disciplines, employ a more neutral interpretation (7, 29, 40). This highlights the potential  
270 importance of metaphors in creating barriers between disciplines.

271

272 As a result of the division between these research communities, certain ideas or approaches  
273 can become confined to different disciplines. For example, the terminology and concept of  
274 global versus local stressors is often mentioned in the marine literature (14, 48, 49) but is  
275 rarely discussed elsewhere. Similarly, it seems that only freshwater ecologists use the term  
276 “reversals” when one stressor reverses the effect of another (5). For instance, Christensen *et*  
277 *al.* (38) found that a positive effect of acidification on phytoplankton became negative when  
278 warming was introduced. Ecotoxicologists have developed considerable theory on null model  
279 selection (24, 50), which is only now being introduced to other communities of multiple-  
280 stressor research (27). Novel concepts and approaches do not need to be (re-)discovered

281 multiple times and all disciplines would benefit from a mutual exchange of ideas. We provide  
 282 a glossary of terms (Table 2), with synonyms grouped, as a step towards the unification of  
 283 multiple-stressor research.

284

285 **Table 2:** *Glossary of widely used terms and concepts in multiple-stressor research. When*  
 286 *multiple terms are grouped together we consider them synonyms.*

Terms/Concepts	Our Definition	Source
<b>Stressor</b>	Any natural or anthropogenic variable that causes a quantifiable change, irrespective of its direction (increase or decrease), in a biological response.	(29)
<b>Factor</b>	However, many researchers associate the term “stressor” with an anthropogenic variable that has a negative impact.	
<b>Driver</b>		
<b>Multiple Stressors</b>	Two or more co-occurring or sequential stressors.	n/a
<b>Combined effect</b>		
<b>Cumulative effect</b>	The aggregate effect of multiple stressors and their interactions.	n/a
<b>Net effect</b>		
<b>Stressor Interaction</b>	Modification of a stressor’s intensity or the sensitivity of an organism or ecosystem towards this stressor by another stressor or multiple other stressors. Thus, the term refers to the interaction between stressors in the real world. By contrast, concepts such as the multiplicative null model rely on mathematical interactions that do not necessarily imply interactions in the real world. Not to be confused with biotic interactions among organisms.	(27)
<b>Additive</b>	When the combined effect of multiple stressors is equal to the sum of their individual effects, i.e. no interaction effect.	(8)
<b>Antagonistic</b>		
<b>Dampening</b>	Interactions between stressors that result in a lesser combined effect than that predicted by a null model (i.e. an interaction between stressors making their observed net effect less than expected).	(27)
<b>Counteracting</b>		
<b>Synergistic</b>		
<b>Amplifying</b>	Interactions between stressors that result in a greater combined effect than that predicted by a null model (i.e. an interaction between stressors making their observed net effect more than expected).	(27)
<b>Reversal</b>	Interactions that result in the combined effect of two stressors being opposite in direction (negative or positive) from that of the sum of their single effects.	(5)
<b>Null Models</b>	A model that predicts the combined effect of multiple stressors assuming the absence of interactions among stressors as defined above. However, some null models contain mathematical interactions to capture stochastic aspects in the action of two stressors, for example the multiplicative null model.	(27)

<b>Ecological Surprises</b>	Scenarios where the mechanisms of stressor interactions are not understood and predictions based on null models fail.	(51)
<b>Discipline</b>	A field of science that is represented by specific journals and conferences and consequently establishes a community of scientists. Disciplines are typically taught and researched separately as part of higher education.	n/a

287

288

289 **4. Towards a Unified Research Framework**

290 Despite the division between disciplines described above, all multiple-stressor researchers  
 291 share the same goals. Elements of these common goals have been identified before but are  
 292 scattered across the literature in both primary research and reviews. Here we integrate and  
 293 develop on these shared research goals of increased (i) ecological complexity, (ii) temporal  
 294 scale and realism, and (iii) prediction. Our conceptual framework offers a future direction for  
 295 multiple-stressor research (Figure 3). Greater interdisciplinary knowledge-exchange,  
 296 facilitated by this review, is a key component of this framework.

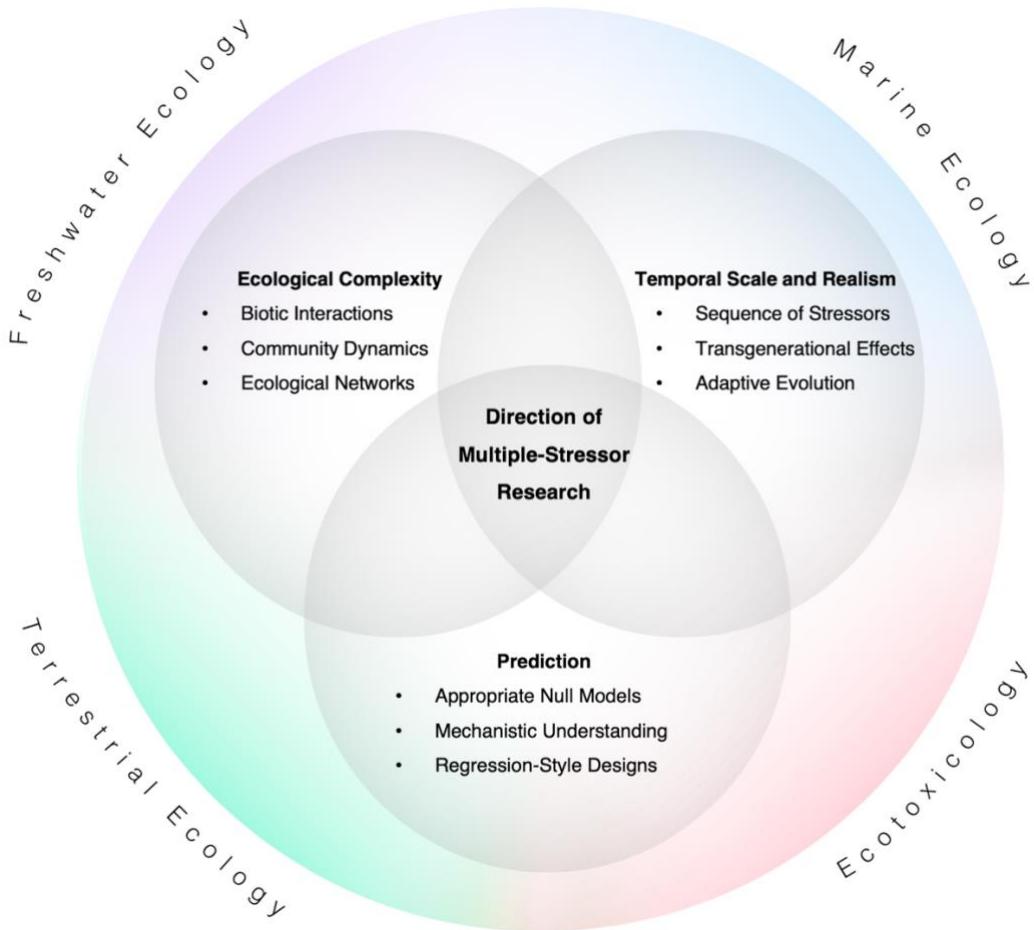
297

298 **4.1 Ecological Complexity**

299 Multiple-stressor research needs to shift its focus towards higher levels of biological  
 300 organization as ecosystem managers are primarily interested in the effect of stressors on  
 301 communities and ecosystems (25, 51). Researchers have called for this increase in ecological  
 302 complexity in freshwater (52, 53), marine (31, 54) and terrestrial (26) ecology as well as in  
 303 ecotoxicology (55). A key question is to what extent species interactions explain statistical  
 304 interactions between stressors themselves at the community and ecosystem level.

305

306



307

308 ***Figure 3:*** An integrative conceptual framework of research goals shared by all disciplines,  
 309 highlighting the future direction of multiple-stressor research.

310

311 Several different approaches have been taken to evaluate the roles of species interactions and  
 312 level of organisation in responses to multiple stressors. For example, in their review of 171  
 313 multiple-stressor studies in marine and coastal ecosystems, Crain *et al.* (3) found that  
 314 synergism was most common in population-level studies, but antagonism was most common  
 315 in community-level studies. Similarly, Côté *et al.* (29) found that synergism became less  
 316 common as biological scale increased in their quantitative review across disciplines.  
 317 However, Jackson *et al.* (5) found no significant difference in the frequencies of interaction  
 318 types at the different biological levels in their review of freshwater studies. Moving beyond  
 319 this “vote-counting” approach, researchers have conducted specific experimental (56, 57) and

320 modelling (58, 59) research on this topic. For example, Galic *et al.* (58) used population  
321 models to show that hypothetical stressors with different modes of action primarily interacted  
322 antagonistically at the individual level but synergistically at the population level.

323

324 Some theory has been developed to predict the impacts of multiple stressors at higher levels  
325 of organisation (25, 51). De Laender (51) showed how competition for common resources can  
326 lead to both synergistic and antagonistic effects of multiple stressors on species richness. In  
327 general, the combined effect of multiple stressors can be amplified at the community level  
328 when stressors act on influential groups such as keystone species or ecosystem engineers (41,  
329 60). Likewise, biotic interactions can mitigate the effect of stressors (e.g., 61, 62). For  
330 example, a modelling study showed that negative interactions among species (e.g.,  
331 competition) increased the net negative effects of external stressors on community-level  
332 properties while positive species interactions (e.g. mutualism) lessened negative impacts (40).

333

334 Interspecific interactions may themselves change after exposure to stressors. For example,  
335 stressors may influence resource competition (63) and may change the susceptibility of hosts  
336 to pathogens and parasites (64, 65). Equally, stressors can alter the trophic relationships of  
337 species (56, 66). Schrama *et al.* (67) applied multiple pesticides to pond mesocosms and used  
338 stable isotope analysis to show that these stressors and their interactions modified the flow of  
339 energy through the food web by inducing shifts in trophic links. Furthermore, biotic  
340 interactions can themselves act as stressors and consequently interact with other stressors. For  
341 instance, the interactions between climate change and ungulate herbivory modulate effects on  
342 forest ecosystems (e.g., 68).

343

344 The importance of biotic interactions in understanding the effects of stressors highlights the  
345 need for an ecological network approach towards multiple-stressor studies (69).  
346 Developments in technologies such as DNA metabarcoding and stable isotope analysis are  
347 improving our ability to detect and quantify biotic interactions (70, 71). With these  
348 technologies, multiple-stressor researchers will be able to clarify to what degree biotic  
349 interactions mediate the statistical interactions between stressors and to ultimately determine  
350 how we understand and predict the effects of multiple stressors.

351

## 352 **4.2 Temporal Scale and Realism**

353 The combined effects of stressors depend on various, largely overlooked, factors related to  
354 different time scales (29, 30). At the time scale within one generation, several temporal  
355 factors have been identified that may determine responses to multiple stressors. First, the  
356 sequence of exposure to stressors may be crucial. For example, the order of exposure of two  
357 toxicants determined their combined effect on *Gammarus pulex* (72). Here, if species'  
358 responses to stressors are negatively correlated, sequence of exposure may be more important  
359 than if their responses are positively correlated (23). Specifically, if paired stressors each  
360 exert a different effect on species, order of exposure may be more important than if their  
361 effects are redundant. Second, the time interval between stressors may influence their  
362 combined impact. Gunderson *et al.* (30) developed a conceptual framework that predicts the  
363 interaction type between sequential exposure to two stressors to be additive when the time  
364 interval between exposure is long, but synergistic when time interval is short. Notably, there  
365 may also be a time lag between the simultaneous exposure to two stressors and the synergistic  
366 effect. For example, combined exposure to both warming and a pollutant in the larval stage of  
367 a damselfly generated a strong synergistic effect across metamorphosis by reducing adult  
368 lifespan (73). Interactions between stressors can also depend on the developmental stage of an

369 organism. Indeed, interactive effects may change, and even reverse, throughout ontogeny.  
370 Przeslawski *et al.* (45) showed in a meta-analysis of marine organisms that the combination of  
371 thermal and salinity stress was more likely to be synergistic for embryonic than for larval life  
372 stages, yet the opposite pattern occurred between thermal and pH stress. Few studies,  
373 however, have tested variation in interactions across developmental stages within the same  
374 species (but see: 74).

375

376 At the time scale of a few generations, little is known about how the interaction type between  
377 stressors in offspring depends on the exposure of the parents to those stressors. As a rare  
378 example, a synergistic interaction between warming and a pollutant was detected in the  
379 mosquito *Culex pipiens* both in the parents and in the offspring of parents exposed to none or  
380 a single stressor. By contrast, an additive effect was present in the offspring of parents  
381 exposed to both stressors simultaneously, because in this condition the pesticide was already  
382 more lethal at the lower temperature (75). At the time scale of tens of generations, the  
383 evolution of adaptation to a stressor may shape tolerance to subsequent stressors because of  
384 pleiotropic effects where the same set of genes contributes to tolerance against different  
385 stressors. This may cause co-tolerance where the acquisition of genetic adaptation to one  
386 stressor increases tolerance to another (76), which is likely as genetic mechanisms of  
387 tolerance to stressors are often conserved (77). Yet, pleiotropic effects may also be  
388 antagonistic resulting in adaptive evolution to one stressor actually reducing tolerance to a  
389 second (78). It is important to note that adaptation (79) and acclimatization (80) to a stressor  
390 may come at a fitness cost. Finally, at a time scale of hundreds of generations, evolution of  
391 thermal tolerance of a damselfly most likely resulted in the synergistic interaction between  
392 warming and a pollutant in high-latitude populations to become additive in low-latitude  
393 populations (81).

394

395 Experiments should attempt to use realistic timing of stressors over meaningful timescales  
396 (e.g., 82), but this can be impractical, and observational studies may need to fill this gap (83).  
397 Furthermore, certain stressors, for example nitrogen deposition (84), accumulate over time,  
398 which can delay ecological effects and further complicate multiple-stressor predictions.  
399 Importantly, the background variation under ambient conditions needs to be considered: a  
400 recent example from plant communities showed that ambient changes may actually outweigh  
401 the impact of stressors over time (85). Understanding if and how interactions between  
402 stressors can change over time is a goal shared by all disciplines.

403

#### 404 **4.3 Prediction**

405 The ultimate goal of multiple-stressor research is prediction of the combined effect of  
406 stressors. This would allow for the incorporation of multiple-stressor research into a risk  
407 assessment framework (86). Over the past twenty years a vast amount of research has been  
408 conducted to test the effects of specific combinations of stressors on specific response  
409 variables. However, very few, if any, general patterns have emerged from meta-analyses (3-6,  
410 17, 18). This approach to studying multiple stressors, calculating proportions of interaction  
411 types across different environments, conditions and responses, does not improve our  
412 predictive capacity of multiple stressors for a variety of reasons, including the existence of a  
413 publication bias towards synergism (29). Furthermore, the results are often context-dependent  
414 (41) and prevent generalization, apart from the fact that non-additivity between stressors is  
415 common.

416

417 To advance research of multiple stressors, there is a need to move beyond comparing  
418 proportions of interaction types and shift focus towards improving our mechanistic

419 understanding of stressor interactions. A shift towards regression-style experimental designs  
420 would enhance our understanding of stressor-response relationships, thus increasing our  
421 ability to predict threshold responses (87, 88). When predicting the combined effects of  
422 multiple stressors, it is important to consider both the modes of action of stressors and their  
423 interactions. For example, the similarity or dissimilarity of stressors' modes of action may  
424 reveal important information about how they may interact (8, 23). Equally, according to Boyd  
425 and Brown (31), there are multiple modes of interaction between stressors at the physico-  
426 chemical, organismal, and ecosystem levels. This concept, of statistical interactions between  
427 stressors occurring as a result of interactions between stressors at different scales, is gaining  
428 more attention (e.g., 41, 54).

429

430 A major issue that needs to be resolved is the use of null models. The additive null model has  
431 been widely used, but also widely criticized for being inappropriate in many scenarios (29).  
432 For example, it is biased towards antagonism when metrics with a fixed boundary, such as  
433 mortality, are used as response variables (8, 17). Many null models can be useful for multiple-  
434 stressor researchers, including both established models from the ecotoxicological literature  
435 and new developments such as the *Stress Addition Model* (24) and the *Compositional Null  
436 Model* (25). Researchers need to be aware of the different null models available and their  
437 association with statistical tests (55). A recent framework for a mechanistic basis to null  
438 model selection aims to facilitate a shift towards a more predictive approach (27). The  
439 objective is to use null models that accurately predict the combined effects of stressors.  
440 "Ecological surprises" arise when our null models are wrong, and researchers are unable to  
441 explain why. Debate over null models and the emerging publications have almost entirely  
442 bypassed the terrestrial global change research community, even though such considerations  
443 could influence the interpretation of some of their findings considerably. Predicting the

444 impacts of multiple stressors is a common goal shared by all disciplines, and achieving this  
445 goal is vital for the sustainable management of resources and for the conservation of  
446 biodiversity and ecosystem services.

447

448 **5. Conclusions**

449 Multiple-stressor researchers from different disciplines are clearly separated. This was  
450 identified during our cross-disciplinary review and was confirmed using bibliometric analysis.  
451 The use of different terminology for predictor variables and for interactions between those  
452 variables has reinforced this separation. Common terminology, or at least awareness of the  
453 different terms in online searches and meta-analyses, would greatly enhance cross-  
454 disciplinary collaboration and would encourage the integration of multiple-stressor research  
455 into mainstream ecology. In fact, our conclusion that researchers should be aware of  
456 terminology from different disciplines applies to all ecological research.

457

458 In future work, researchers should consider multiple-stressor literature from other disciplines  
459 for guidance on methods and analyses. Authors of primary research should include multiple  
460 terms in their keyword section to enhance the visibility of their research. However, limits on  
461 the number of keywords in journals may incentivize authors to only use keywords relevant to  
462 their own discipline. Meta-analyses of the multiple-stressor literature should consider the  
463 broader range of terminology identified in this review (see common glossary: Table 2) and,  
464 where possible, be repeated to include relevant but previously missed studies. Multiple-  
465 stressor research is moving forward with all disciplines converging towards the same  
466 common goals, and the time is ripe for a unified approach. Division between ecosystem types  
467 and disciplines is largely a human creation. Species and stressors cross these borders, and so  
468 should the scientists who study them.

469 **Acknowledgements:**

470 This manuscript is the product of a cross-disciplinary workshop, *StressNet*, intended to bridge  
471 the gaps among the different disciplines studying the impacts of multiple stressors.

472

473

474 **Funding:**

475 J.A.O. was funded by an Irish Research Council Laureate Award (IRCLA/2017/112) and  
476 TCD Provost's PhD Award held by J.J.P. during the writing of this review. R.B.S. received  
477 funding for the *StressNet* workshop from the DFG and the University of Koblenz-Landau.

478

479

480 **References:**

481 1. Urban MC. Accelerating extinction risk from climate change. *Science*.  
482 2015;348(6234):571-3.

483 2. Dirzo R, Young HS, Galetti M, Ceballos G, Isaac NJ, Collen B. Defaunation in the  
484 Anthropocene. *Science*. 2014;345(6195):401-6.

485 3. Crain CM, Kroeker K, Halpern BS. Interactive and cumulative effects of multiple  
486 human stressors in marine systems. *Ecology Letters*. 2008;11(12):1304-15.

487 4. Dieleman WI, Vicca S, Dijkstra FA, Hagedorn F, Hovenden MJ, Larsen KS, et al.  
488 Simple additive effects are rare: a quantitative review of plant biomass and soil process  
489 responses to combined manipulations of CO<sub>2</sub> and temperature. *Global Change Biology*.  
490 2012;18(9):2681-93.

491 5. Jackson MC, Loewen CJ, Vinebrooke RD, Chimimba CT. Net effects of multiple  
492 stressors in freshwater ecosystems: a meta-analysis. *Global Change Biology*. 2016;22(1):180-  
493 9.

- 494 6. Holmstrup M, Bindesbøl A-M, Oostingh GJ, Duschl A, Scheil V, Köhler H-R, et al.  
495 Interactions between effects of environmental chemicals and natural stressors: a review.  
496 Science of the Total Environment. 2010;408(18):3746-62.
- 497 7. Piggott JJ, Townsend CR, Matthaei CD. Reconceptualizing synergism and antagonism  
498 among multiple stressors. Ecology and Evolution. 2015;5(7):1538-47.
- 499 8. Folt C, Chen C, Moore M, Burnaford J. Synergism and antagonism among multiple  
500 stressors. Limnology and Oceanography. 1999;44(3part2):864-77.
- 501 9. Bliss C. The toxicity of poisons applied jointly. Annals of Applied Biology.  
502 1939;26(3):585-615.
- 503 10. Loewe S, Muischnek H. Über Kombinationswirkungen. Naunyn-Schmiedebergs  
504 Archiv für experimentelle Pathologie und Pharmakologie. 1926;114(5-6):313-26.
- 505 11. Andersen JH, Berzaghi F, Christensen T, Geertz-Hansen O, Mosbech A, Stock A, et  
506 al. Potential for cumulative effects of human stressors on fish, sea birds and marine mammals  
507 in Arctic waters. Estuarine, Coastal and Shelf Science. 2017;184:202-6.
- 508 12. Lenihan HS, Peterson CH, Miller RJ, Kayal M, Potoski M. Biotic disturbance  
509 mitigates effects of multiple stressors in a marine benthic community. Ecosphere.  
510 2018;9(6):e02314.
- 511 13. Salis R, Bruder A, Piggott J, Summerfield T, Matthaei C. High-throughput amplicon  
512 sequencing and stream benthic bacteria: identifying the best taxonomic level for multiple-  
513 stressor research. Scientific Reports. 2017;7:44657.
- 514 14. Strain EM, van Belzen J, van Dalen J, Bouma TJ, Airolidi L. Management of local  
515 stressors can improve the resilience of marine canopy algae to global stressors. PLoS One.  
516 2015;10(3):e0120837.
- 517 15. Kaunisto S, Ferguson LV, Sinclair BJ. Can we predict the effects of multiple stressors  
518 on insects in a changing climate? Current Opinion in Insect Science. 2016;17:55-61.
- 519 16. Boone MD, Semlitsch RD, Little EE, Doyle MC. Multiple stressors in amphibian  
520 communities: effects of chemical contamination, bullfrogs, and fish. Ecological Applications.  
521 2007;17(1):291-301.

- 522 17. Lange K, Bruder A, Matthaei CD, Brodersen J, Paterson RA. Multiple-stressor effects  
523 on freshwater fish: Importance of taxonomy and life stage. *Fish and Fisheries*. 2018.
- 524 18. Yue K, Fornara DA, Yang W, Peng Y, Li Z, Wu F, et al. Effects of three global  
525 change drivers on terrestrial C: N: P stoichiometry: a global synthesis. *Global Change  
526 Biology*. 2017;23(6):2450-63.
- 527 19. Larsen KS, Andresen LC, Beier C, Jonasson S, Albert KR, Ambus P, et al. Reduced N  
528 cycling in response to elevated CO<sub>2</sub>, warming, and drought in a Danish heathland:  
529 synthesizing results of the CLIMAITE project after two years of treatments. *Global Change  
530 Biology*. 2011;17(5):1884-99.
- 531 20. Rillig MC, Ryo M, Lehmann A, Aguilar-Trigueros CA, Buchert S, Wulf A, et al. The  
532 role of multiple global change factors in driving soil functions and microbial biodiversity.  
533 *Science*. 2019;366(6467):886-90.
- 534 21. Laskowski R, Bednarska AJ, Kramarz PE, Loureiro S, Scheil V, Kudłek J, et al.  
535 Interactions between toxic chemicals and natural environmental factors—A meta-analysis and  
536 case studies. *Science of the Total Environment*. 2010;408(18):3763-74.
- 537 22. Moe SJ, De Schamphelaere K, Clements WH, Sorensen MT, Van den Brink PJ, Liess  
538 M. Combined and interactive effects of global climate change and toxicants on populations  
539 and communities. *Environmental Toxicology and Chemistry*. 2013;32(1):49-61.
- 540 23. Vinebrooke RD, Cottingham KL, Norberg MS, Dodson SI, Maberly SC, Sommer U.  
541 Impacts of multiple stressors on biodiversity and ecosystem functioning: the role of species  
542 co-tolerance. *Oikos*. 2004;104(3):451-7.
- 543 24. Liess M, Foit K, Knillmann S, Schäfer RB, Liess H-D. Predicting the synergy of  
544 multiple stress effects. *Scientific Reports*. 2016;6:32965.
- 545 25. Thompson PL, MacLennan MM, Vinebrooke RD. An improved null model for  
546 assessing the net effects of multiple stressors on communities. *Global Change Biology*.  
547 2018;24(1):517-25.

- 548 26. Leuzinger S, Luo Y, Beier C, Dieleman W, Vicca S, Körner C. Do global change  
549 experiments overestimate impacts on terrestrial ecosystems? *Trends in Ecology & Evolution*.  
550 2011;26(5):236-41.
- 551 27. Schäfer RB, Piggott JJ. Advancing understanding and prediction in multiple stressor  
552 research through a mechanistic basis for null models. *Global Change Biology*.  
553 2018;24(5):1817-26.
- 554 28. Darling ES, Côté IM. Quantifying the evidence for ecological synergies. *Ecology*  
555 Letters. 2008;11(12):1278-86.
- 556 29. Côté IM, Darling ES, Brown CJ. Interactions among ecosystem stressors and their  
557 importance in conservation. *Proceedings of the Royal Society B*. 2016;283(1824):20152592.
- 558 30. Gunderson AR, Armstrong EJ, Stillman JH. Multiple stressors in a changing world:  
559 the need for an improved perspective on physiological responses to the dynamic marine  
560 environment. *Annual Review of Marine Science*. 2016;8:357-78.
- 561 31. Boyd PW, Brown CJ. Modes of interactions between environmental drivers and  
562 marine biota. *Frontiers in Marine Science*. 2015;2:9.
- 563 32. Sirami C, Caplat P, Popov S, Clamens A, Arlettaz R, Jiguet F, et al. Impacts of global  
564 change on species distributions: Obstacles and solutions to integrate climate and land use.  
565 *Global Ecology and Biogeography*. 2017;26(4):385-94.
- 566 33. Harvey BP, Gwynn-Jones D, Moore PJ. Meta-analysis reveals complex marine  
567 biological responses to the interactive effects of ocean acidification and warming. *Ecology*  
568 and Evolution. 2013;3(4):1016-30.
- 569 34. Zhou L, Zhou X, Shao J, Nie Y, He Y, Jiang L, et al. Interactive effects of global  
570 change factors on soil respiration and its components: a meta-analysis. *Global Change  
571 Biology*. 2016;22(9):3157-69.
- 572 35. Menge BA, Chan F, Dudas S, Eerkes-Medrano D, Grorud-Colvert K, Heiman K, et al.  
573 Terrestrial ecologists ignore aquatic literature: asymmetry in citation breadth in ecological  
574 publications and implications for generality and progress in ecology. *Journal of Experimental  
575 Marine Biology and Ecology*. 2009;377(2):93-100.

- 576 36. Knapp S, Schweiger O, Kraberg A, Asmus H, Asmus R, Brey T, et al. Do drivers of  
577 biodiversity change differ in importance across marine and terrestrial systems—Or is it just  
578 different research communities' perspectives? *Science of the Total Environment*.  
579 2017;574:191-203.
- 580 37. Van Eck N, Waltman L. Software survey: VOSviewer, a computer program for  
581 bibliometric mapping. *Scientometrics*. 2009;84(2):523-38.
- 582 38. Christensen MR, Graham MD, Vinebrooke RD, Findlay DL, Paterson MJ, Turner  
583 MA. Multiple anthropogenic stressors cause ecological surprises in boreal lakes. *Global  
584 Change Biology*. 2006;12(12):2316-22.
- 585 39. Boyd PW, Hutchins DA. Understanding the responses of ocean biota to a complex  
586 matrix of cumulative anthropogenic change. *Marine Ecology Progress Series*. 2012;470:125-  
587 35.
- 588 40. Thompson PL, MacLennan MM, Vinebrooke RD. Species interactions cause non-  
589 additive effects of multiple environmental stressors on communities. *Ecosphere*.  
590 2018;9(11):e02518.
- 591 41. Kroeker KJ, Kordas RL, Harley CD. Embracing interactions in ocean acidification  
592 research: confronting multiple stressor scenarios and context dependence. *Biology Letters*.  
593 2017;13(3):20160802.
- 594 42. Townsend CR, Uhlmann SS, Matthaei CD. Individual and combined responses of  
595 stream ecosystems to multiple stressors. *Journal of Applied Ecology*. 2008;45(6):1810-9.
- 596 43. Ormerod SJ, Dobson M, Hildrew AG, Townsend C. Multiple stressors in freshwater  
597 ecosystems. *Freshwater Biology*. 2010;55:1-4.
- 598 44. Hering D, Carvalho L, Argillier C, Beklioglu M, Borja A, Cardoso AC, et al.  
599 Managing aquatic ecosystems and water resources under multiple stress—An introduction to  
600 the MARS project. *Science of the Total Environment*. 2015;503:10-21.
- 601 45. Przeslawski R, Byrne M, Mellin C. A review and meta-analysis of the effects of  
602 multiple abiotic stressors on marine embryos and larvae. *Global Change Biology*.  
603 2015;21(6):2122-40.

- 604 46. Borer ET, Seabloom EW, Gruner DS, Harpole WS, Hillebrand H, Lind EM, et al.  
605 Herbivores and nutrients control grassland plant diversity via light limitation. *Nature*.  
606 2014;508(7497):517.
- 607 47. Gruner DS, Smith JE, Seabloom EW, Sandin SA, Ngai JT, Hillebrand H, et al. A  
608 cross-system synthesis of consumer and nutrient resource control on producer biomass.  
609 *Ecology Letters*. 2008;11(7):740-55.
- 610 48. Russell BD, Connell SD. Origins and consequences of global and local stressors:  
611 incorporating climatic and non-climatic phenomena that buffer or accelerate ecological  
612 change. *Marine Biology*. 2012;159(11):2633-9.
- 613 49. Brown CJ, Saunders MI, Possingham HP, Richardson AJ. Managing for interactions  
614 between local and global stressors of ecosystems. *PloS One*. 2013;8(6):e65765.
- 615 50. Backhaus T, Faust M. Predictive environmental risk assessment of chemical mixtures:  
616 a conceptual framework. *Environmental Science & Technology*. 2012;46(5):2564-73.
- 617 51. De Laender F. Community- and ecosystem-level effects of multiple environmental  
618 change drivers: beyond null model testing. *Global Change Biology*. 2018.
- 619 52. Bray J, Reich J, Nichols S, Kon Kam King G, Mac Nally R, Thompson R, et al.  
620 Biological interactions mediate context and species-specific sensitivities to salinity.  
621 *Philosophical Transactions of the Royal Society B*. 2018;374(1764):20180020.
- 622 53. Schuwirth N, Dietzel A, Reichert P. The importance of biotic interactions for the  
623 prediction of macroinvertebrate communities under multiple stressors. *Functional Ecology*.  
624 2016;30(6):974-84.
- 625 54. Griffen BD, Belgrad BA, Cannizzo ZJ, Knotts ER, Hancock ER. Rethinking our  
626 approach to multiple stressor studies in marine environments. *Marine Ecology Progress Series*.  
627 2016;543:273-81.
- 628 55. Van den Brink PJ, Boxall AB, Maltby L, Brooks BW, Rudd MA, Backhaus T, et al.  
629 Toward sustainable environmental quality: Priority research questions for Europe.  
630 *Environmental Toxicology and Chemistry*. 2018;37(9):2281-95.

- 631 56. Bruder A, Salis RK, Jones PE, Matthaei CD. Biotic interactions modify multiple-  
632 stressor effects on juvenile brown trout in an experimental stream food web. Global Change  
633 Biology. 2017;23(9):3882-94.
- 634 57. O'Gorman EJ, Fitch JE, Crowe TP. Multiple anthropogenic stressors and the structural  
635 properties of food webs. Ecology. 2012;93(3):441-8.
- 636 58. Galic N, Sullivan LL, Grimm V, Forbes VE. When things don't add up: quantifying  
637 impacts of multiple stressors from individual metabolism to ecosystem processing. Ecology  
638 Letters. 2018;21(4):568-77.
- 639 59. Griffith GP, Strutton PG, Semmens JM, Fulton EA. Identifying important species that  
640 amplify or mitigate the interactive effects of human impacts on marine food webs.  
641 Conservation Biology. 2019;33(2):403-12.
- 642 60. Gooding RA, Harley CD, Tang E. Elevated water temperature and carbon dioxide  
643 concentration increase the growth of a keystone echinoderm. Proceedings of the National  
644 Academy of Sciences. 2009;106(23):9316-21.
- 645 61. Bulleri F, Eriksson BK, Queirós A, Airoldi L, Arenas F, Arvanitidis C, et al.  
646 Harnessing positive species interactions as a tool against climate-driven loss of coastal  
647 biodiversity. PLoS Biology. 2018;16(9):e2006852.
- 648 62. Piscart C, Webb D, Beisel JN. An acanthocephalan parasite increases the salinity  
649 tolerance of the freshwater amphipod *Gammarus roeseli* (Crustacea: Gammaridae). The  
650 Science of Nature. 2007;94(9):741-7.
- 651 63. Kroeker KJ, Micheli F, Gambi MC. Ocean acidification causes ecosystem shifts via  
652 altered competitive interactions. Nature Climate Change. 2013;3(2):156.
- 653 64. Lafferty KD, Holt RD. How should environmental stress affect the population  
654 dynamics of disease? Ecology Letters. 2003;6(7):654-64.
- 655 65. Lenihan HS, Micheli F, Shelton SW, Peterson CH. The influence of multiple  
656 environmental stressors on susceptibility to parasites: an experimental determination with  
657 oysters. Limnology and Oceanography. 1999;44(3):910-24.

- 658 66. Arnold T, Mealey C, Leahey H, Miller AW, Hall-Spencer JM, Milazzo M, et al.  
659 Ocean acidification and the loss of phenolic substances in marine plants. PLoS One.  
660 2012;7(4):e35107.
- 661 67. Schrama M, Barmentlo SH, Hunting ER, van Logtestijn RS, Vijver MG, van  
662 Bodegom PM. Pressure-induced shifts in trophic linkages in a simplified aquatic food web.  
663 Frontiers in Environmental Science. 2017;5:75.
- 664 68. Didion M, Kupferschmid A, Wolf A, Bugmann H. Ungulate herbivory modifies the  
665 effects of climate change on mountain forests. Climatic Change. 2011;109(3-4):647-69.
- 666 69. Bruder A, Frainer A, Rota T, Primicerio R. The importance of ecological networks in  
667 multiple-stressor research and management. Frontiers in Environmental Science. 2019;7:59.
- 668 70. Layman CA, Araujo MS, Boucek R, Hammerschlag-Peyer CM, Harrison E, Jud ZR,  
669 et al. Applying stable isotopes to examine food-web structure: an overview of analytical tools.  
670 Biological Reviews. 2012;87(3):545-62.
- 671 71. Roslin T, Majaneva S. The use of DNA barcodes in food web construction—terrestrial  
672 and aquatic ecologists unite! Genome. 2016;59(9):603-28.
- 673 72. Ashauer R, O'Connor I, Escher BI. Toxic Mixtures in Time - The Sequence Makes  
674 the Poison. Environmental Science & Technology. 2017;51(5):3084-92.
- 675 73. Debecker S, Dinh KV, Stoks R. Strong delayed interactive effects of metal exposure  
676 and warming: latitude-dependent synergisms persist across metamorphosis. Environmental  
677 Science & Technology. 2017;51(4):2409-17.
- 678 74. Fitzgerald JA, Katsiadaki I, Santos EM. Contrasting effects of hypoxia on copper  
679 toxicity during development in the three-spined stickleback (*Gasterosteus aculeatus*).  
680 Environmental Pollution. 2017;222:433-43.
- 681 75. Tran TT, Janssens L, Dinh KV, Stoks R. Transgenerational interactions between  
682 pesticide exposure and warming in a vector mosquito. Evolutionary Applications. 2018.
- 683 76. Bubliy O, Loeschke V. Correlated responses to selection for stress resistance and  
684 longevity in a laboratory population of *Drosophila melanogaster*. Journal of Evolutionary  
685 Biology. 2005;18(4):789-803.

- 686 77. Sikkink KL, Reynolds RM, Cresko WA, Phillips PC. Environmentally induced  
687 changes in correlated responses to selection reveal variable pleiotropy across a complex  
688 genetic network. *Evolution*. 2015;69(5):1128-42.
- 689 78. Hua J, Wuerthner VP, Jones DK, Mattes B, Cothran RD, Relyea RA, et al. Evolved  
690 pesticide tolerance influences susceptibility to parasites in amphibians. *Evolutionary  
691 Applications*. 2017;10(8):802-12.
- 692 79. Hoffmann AA, Sørensen JG, Loeschke V. Adaptation of *Drosophila* to temperature  
693 extremes: bringing together quantitative and molecular approaches. *Journal of Thermal  
694 Biology*. 2003;28(3):175-216.
- 695 80. Goussen B, Price OR, Rendal C, Ashauer R. Integrated presentation of ecological risk  
696 from multiple stressors. *Scientific Reports*. 2016;6:36004.
- 697 81. Dinh Van K, Janssens L, Debecker S, De Jonge M, Lambret P, Nilsson-Örtman V, et  
698 al. Susceptibility to a metal under global warming is shaped by thermal adaptation along a  
699 latitudinal gradient. *Global Change Biology*. 2013;19(9):2625-33.
- 700 82. Cheng BS, Bible JM, Chang AL, Ferner MC, Wasson K, Zabin CJ, et al. Testing local  
701 and global stressor impacts on a coastal foundation species using an ecologically realistic  
702 framework. *Global Change Biology*. 2015;21(7):2488-99.
- 703 83. Hättenschwiler S, Miglietta F, Raschi A, Körner C. Thirty years of in situ tree growth  
704 under elevated CO<sub>2</sub>: a model for future forest responses? *Global Change Biology*.  
705 1997;3(5):463-71.
- 706 84. Payne RJ, Campbell C, Britton AJ, Mitchell RJ, Pakeman RJ, Jones L, et al. What is  
707 the most ecologically-meaningful metric of nitrogen deposition? *Environmental Pollution*.  
708 2019;247:319-31.
- 709 85. Langley JA, Chapman SK, La Pierre KJ, Avolio M, Bowman WD, Johnson DS, et al.  
710 Ambient changes exceed treatment effects on plant species abundance in global change  
711 experiments. *Global Change Biology*. 2018;24(12):5668-79.

- 712 86. Van den Brink PJ, Choung CB, Landis W, Mayer-Pinto M, Pettigrove V, Scanes P, et  
713 al. New approaches to the ecological risk assessment of multiple stressors. *Marine and*  
714 *Freshwater Research.* 2016;67(4):429-39.
- 715 87. Kreyling J, Schweiger AH, Bahn M, Ineson P, Migliavacca M, Morel-Journel T, et al.  
716 To replicate, or not to replicate—that is the question: how to tackle nonlinear responses in  
717 ecological experiments. *Ecology Letters.* 2018;21(11):1629-38.
- 718 88. Boyd PW, Collins S, Dupont S, Fabricius K, Gattuso JP, Havenhand J, et al.  
719 Experimental strategies to assess the biological ramifications of multiple drivers of global  
720 ocean change—a review. *Global Change Biology.* 2018;24(6):2239-61.
- 721