nature ecology & evolution

ARTICLES

https://doi.org/10.1038/s41559-020-01370-3

Check for updates

Impacts of hypoxic events surpass those of future ocean warming and acidification

Eduardo Sampaio[1,2,3]✉, Catarina Santos[1], Inês C. Rosa[1], Verónica Ferreira[4], Hans-Otto Pörtner[5], Carlos M. Duarte[6], Lisa A. Levin[7] and Rui Rosa[1]

Over the past decades, three major challenges to marine life have emerged as a consequence of anthropogenic emissions: ocean warming, acidification and oxygen loss. While most experimental research has targeted the first two stressors, the last remains comparatively neglected. Here, we implemented sequential hierarchical mixed-model meta-analyses (721 control–treatment comparisons) to compare the impacts of oxygen conditions associated with the current and continuously intensifying hypoxic events (1–3.5 O_2 mg l^{-1}) with those experimentally yielded by ocean warming (+4 °C) and acidification (−0.4 units) conditions on the basis of IPCC projections (RCP 8.5) for 2100. In contrast to warming and acidification, hypoxic events elicited consistent negative effects relative to control biological performance—survival (−33%), abundance (−65%), development (−51%), metabolism (−33%), growth (−24%) and reproduction (−39%)—across the taxonomic groups (mollusks, crustaceans and fish), ontogenetic stages and climate regions studied. Our findings call for a refocus of global change experimental studies, integrating oxygen concentration drivers as a key factor of ocean change. Given potential combined effects, multistressor designs including gradual and extreme changes are further warranted to fully disclose the future impacts of ocean oxygen loss, warming and acidification.

The global ocean has been shielding our planet from abrupt climate change, by absorbing a large portion of the anthropogenically emitted carbon dioxide (CO_2) and the excess heat trapped in the atmosphere, leading to ocean acidification (OA, decreasing seawater pH) and warming (OW, rising seawater temperatures)[1]. Additionally, oxygen loss in the ocean (OD, ocean deoxygenation) is being exacerbated by OW and reinforced by geophysical and biochemical processes[2–4]. Referred to as the 'deadly trio'[5], these three stressors (OA, OW and OD) are expected to elicit major negative impacts in marine ecosystems over the forthcoming decades[6–8], with consequences for human well-being and socioeconomic prosperity[9–11]. Should society maintain the current trajectory of greenhouse gas emissions (representative concentration pathway, RCP 8.5), according to the IPCC, sea surface pH will decrease by 0.4 units in 2100, temperature will increase by nearly 4 °C and dissolved oxygen will be reduced by 5% (refs. [1,12,13]). In addition to these long-term gradual changes, the frequency, strength and pervasiveness of abrupt events related to the same three factors will also increase. Hence, extreme acidification events (EAEs), marine heatwaves (MHWs) and hypoxic events (HEs) will become more ubiquitous and potentially more devastating[4,14–17].

The development of adequate adaptation and mitigation strategies to deal with these ocean changes is of utmost importance and a well-established priority in the international agenda[18]. As such, the scientific community has directed considerable efforts towards investigating the effects of climate change-related drivers on marine biota[19–21]. Since the 2000s, there has been a remarkable increase in the number of scientific studies addressing the impacts and underlying mechanisms of both OW and OA, in a wide variety of marine organisms (Supplementary Fig. 1). Research shows that OW disrupts key biological processes, from increased energetic demands to shifts in phenological cycles and distributional ranges, with cascading consequences to ecosystem functioning[22,23]. On the other hand, OA is known to impact acid–base regulation, energy allocation and calcification processes of marine organisms by increasing hydrogen ion (H^+) and CO_2 concentrations in body fluids and altering carbonate saturation state[24,25].

In contrast, oxygen loss has attracted far less attention in the scientific community[2,26] (see Supplementary Fig. 1 for comparative publication trends over the last decades). While oxygen loss is known to elicit severely detrimental biological consequences (such as active area avoidance, altered physiology and high mortality rates, including of marine megafauna)[27–30], its effects have been addressed mainly in the context of acute exposure to hypoxia, in a framework more akin to HEs than to gradual OD. This contrasts with most OA and OW experiments, which although short-termed (usually spanning weeks[20,24]), tend to be designed according to the IPCC projections for 2100[1,25]. These distinct approaches substantially increase the uncertainty involved in estimating the full impacts of climate change-related drivers in marine biota. Moreover, very few studies have experimentally investigated the combined action of the 'deadly trio', although these three factors will act concurrently in coming years. Factorial experimental designs have been mostly restricted to OA and OW and tend to report context-dependent interactive (antagonistic or synergistic) or additive effects[25,31,32], further highlighting the need for further empirical investigation.

[1]Marine and Environmental Sciences Centre (MARE), Laboratório Marítimo da Guia, Faculdade de Ciências, Universidade de Lisboa, Cascais, Portugal. [2]Department of Collective Behaviour, Max Planck Institute of Animal Behavior, University of Konstanz, Konstanz, Germany. [3]Centre for the Advanced Study of Collective Behaviour, University of Konstanz, Konstanz, Germany. [4]Marine and Environmental Sciences Centre (MARE), Department of Life Sciences, University of Coimbra, Coimbra, Portugal. [5]Integrative Ecophysiology, Alfred-Wegener-Institut Helmholtz-Zentrum für Polar- und Meeresforschung, Bremerhaven, Germany. [6]Red Sea Research Center (RSRC), King Abdullah University of Science and Technology (KAUST), Thuwal, Saudi Arabia. [7]Center for Marine Biodiversity and Conservation and Integrative Oceanography Division, Scripps Institution of Oceanography, University of California, San Diego, CA, USA. ✉e-mail: easampaio@fc.ul.pt

Here, we integrate existing global change literature and help bridge the knowledge gap around the potential impacts elicited by the looming 'deadly trio' on marine life. First, we establish a comparative framework and analyse how distinct biological responses are impacted by the different stressors. Then, as organisms' vulnerability is largely dictated by their inherent physiological contexts, we address how expected responses to stressors can vary across distinct groups in the marine tree of life (fishes, mollusks and crustaceans), ontogenetic life stages (eggs/larvae, juveniles and adults) and the current abiotic conditions to which organisms are adapted and acclimatized (temperate and tropical). Finally, we discuss limitations in current experimental studies and identify potential improvement pathways. The findings should help to redirect research efforts towards a more integrative and realistic view of the impacts of climate change on the marine biota that would better support decision-making processes for ocean sustainability.

Creating a comparative framework for stressors

To robustly assess differential stressor impacts across taxonomical groups, ontogenetic stages and climate regions, we identified the main bodies of literature produced over the past decades and retrieved data for stressor magnitudes generally used in climate change studies, integrating the available information on OW and OA, with HEs within a hierarchical mixed-model meta-analysis (HMMM) framework. Thus, considering projections for surface waters in the year 2100 in the most extreme widely used scenario (RCP 8.5)[1], OW and OA (as well as OW + OA) were defined by maximum temperature and pH differentials of $\Delta T = +4\,^{\circ}C$ and $\Delta pH = -0.4$ units relative to controls, respectively. We defined HEs on the basis of a fixed interval around ~2 O_2 mg l^{-1} (moderate hypoxia)[17,29,33] and collected experimental data from studies where O_2 concentrations ranging between 1 and 3.5 O_2 mg l^{-1} were used as hypoxia treatment[1,13,28], therefore rejecting extreme hypoxia concentrations (see Methods for detailed discussion on stressor selection criteria).

We retrieved data from 136 papers, corresponding to 721 different control–treatment comparisons, that is experiments (see Supplementary Fig. 2 for a breakdown of included/excluded studies according to criteria). Data were catalogued according to biological responses, stressor magnitude (hereafter 'stressor size'), taxonomical group, species, ontogenetic life stage and climate region (Supplementary Data 1; Data collection in Methods). Using sequential HMMMs (from average to specific responses, see Supplementary Tables), we reanalysed the curated dataset (Supplementary Data 2) and recalculated effect sizes dependent on stressor size for OW, OA, OW + OA and HE (corresponding to four levels in the factor 'Stressor') within the same statistical test, enabling posterior statistical comparisons between these stressors[34,35] (Statistical analyses in Methods). Due to a lack of sufficient studies, computing effects sizes for the combined impacts of HE with OA and OW was not feasible (Supplementary Data 1; Methods). We further stipulated random effects to compute independent, non-correlated effect sizes for the four stressors, considering variation within and between papers and experiments (for example, different experiments performed within each paper).

Using this innovative approach in global change research[36], we calculated independent effect sizes for all stressors (OW, OA, OW + OA and HE) weighted by stressor size and measured differential stressor impacts over an array of biological responses (survival, abundance, growth, metabolism, reproduction and development) and according to: (1) taxonomic groups (fish, mollusk and crustacean); (2) life stages (egg/larva, juvenile and adult); and (3) climate regions (tropical/subtropical and temperate).

Impacts on biological responses

All stressors led to detrimental effects as the average biological response, however HE elicited a stronger effect (−34%) compared to OA (−15%), OW (−16%), and OW + OA (−15%). Moreover, HE consistently inhibited all biological responses: survival (−33%), abundance (−65%), development (−51%), metabolism (−33%), growth (−24%) and reproduction (−39%) (Supplementary Table 1 and Fig. 1). Both the other isolated stressors impacted two of the six biological responses: OW increased metabolism (+13%) and inhibited survival (−32%); while OA inhibited survival (−8%) and development (−16%). Importantly, while OW + OA also affected three of the six biological responses analysed (survival by −20%, reproduction by −14% and development −6%), HE elicited comparatively stronger negative effects in each individual response, except survival where there were no differences between these stressors (Supplementary Table 1 and Fig. 1). Concurrently, HE was the only stressor prompting severe detrimental effects on growth and abundance (specific taxa density). As such, HE-related effects consistently impacted cellular (metabolism and reproduction) and individual biological responses (survival, growth, development and abundance), including fitness-related ones, registering strong effects in two different levels of biological organizations[17].

Impacts across taxonomic groups

From the taxonomic groups studied, we were able to calculate mean effect sizes for fish, mollusks and crustaceans, which rank amongst the groups most vulnerable to global change[17,25,32,37]. HE was again the most relevant inhibitor across the responses studied, as well as the only stressor eliciting significant effects in all combinations analysed for taxonomic groups over biological responses (Supplementary Table 2 and Fig. 2). Averaging all biological responses, aside from HE impacts (−39%, −26% and −40% for crustaceans, mollusks and fishes, respectively), OA inhibited responses in mollusks (−22%), while OW and OW + OA also inhibited average responses in mollusks and in fishes (around −15%). OA effects on survival were restricted to one taxonomical group (crustaceans), whereas OW + OA registered significant effects on the only taxonomical group where estimating effect sizes was possible (crustaceans). OW significantly impacted the survival of crustaceans and mollusks but registered no effect on that of fishes, with confidence intervals suggesting fish have highly variable responses to this stressor (Fig. 2).

It was not possible to compute stressor effects on crustacean growth and metabolism due to lack of sample size. However, growth was inhibited by all stressors in fishes but only by HE in mollusks, while metabolism was stimulated by OW in fishes and consistently inhibited by HE (in both mollusks and fishes). Thus, OW stimulatory effects on metabolism (Figs. 1 and 2, about +25%) did not correlate with positive effects in growth, suggesting that these effects can be classified as adverse, since metabolic costs increased with no positive feedback[7,38]. In general, crustaceans and mollusks appear to be most susceptible to changes in H^+ concentration (which may be linked to calcium carbonate sequestration and damage to exoskeletons and shells[25,39]), whereas fishes are more affected by increases in temperature (possibly due to metabolic costs[40]) or a combination of both drivers[41,42]. Summing up, while effects of OW, OA and their combination occur only within specific biological contexts, HE impacts are pervasive across the taxonomic (heterotrophic) groups and biological responses analysed.

Impacts across ontogeny and climatic regions

Gauging the combined biological response from the same heterotroph groups (fishes, mollusks and crustaceans) according to their climate regions and ontogenetic life stages yielded, once again, universal HE-induced detrimental effects (mean −40%, Fig. 3 and Supplementary Table 3). Concerning ontogenetic life stages, on average and in temperate regions specifically, OW and OW + OA also significantly impacted egg and larval stages, suggesting that the combined effect seems to be mainly driven by OW (around −10%

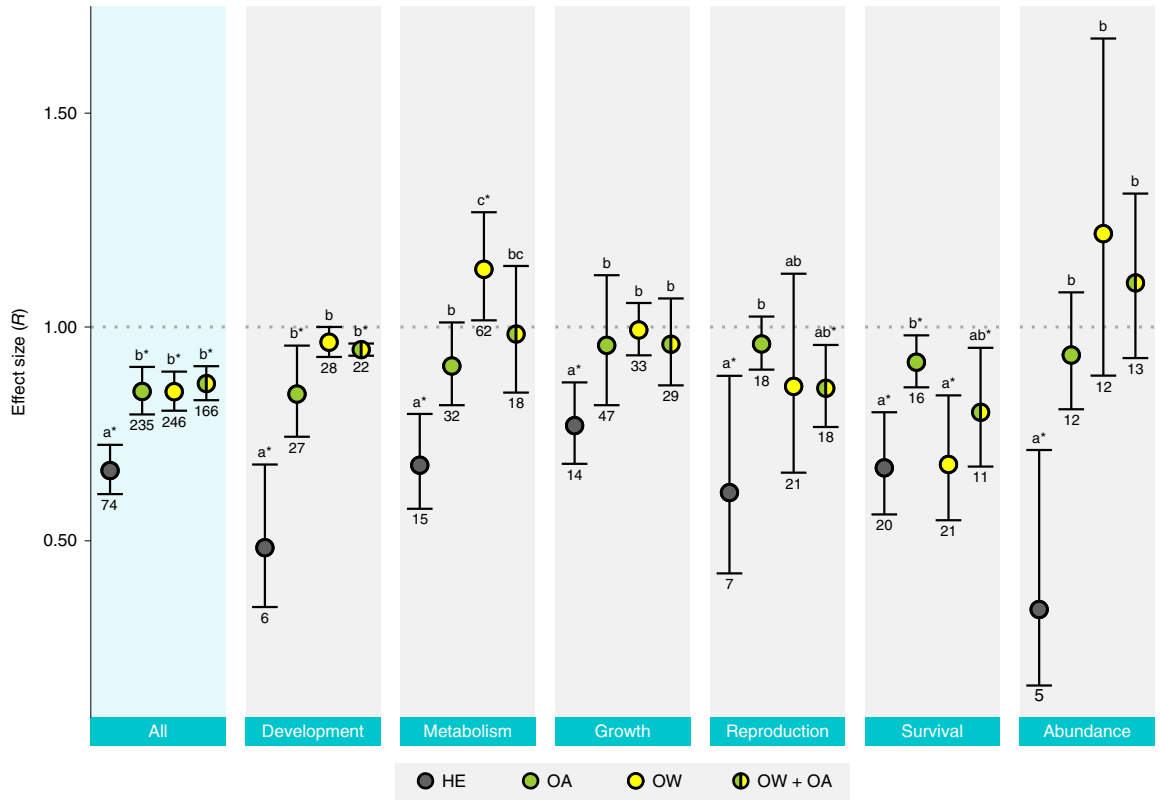

Fig. 1 | Average and detailed biological responses of combined marine biota to global change stressors. Survival, abundance, growth, metabolism, reproduction and development responses of marine biota (combined fish, mollusks, crustaceans, echinoderms and corals) to HE, OA, OW, and OW+OA, taking into account distinct stressor manipulation levels (stressor size). *R* portrays effect size (response ratio) and 95% CI. The dashed line (*R*=1) indicates no effect, while *R*>1 indicates stimulation and *R*<1 indicates inhibition. Asterisks indicate significant effect sizes (HMMMs, 95% CI does not overlap *R*=1), different letters show significant differences among stressors (Tukey HSD tests, *P*<0.05) and numbers indicate sample sizes (number of experiments) for each effect size. Statistical outputs are available in Supplementary Table 1.

for both). However, these early impacts were not registered for more developed ontogenetic stages (juveniles and adults), where only HE registered consistent negative impacts across both averaged and specific climate regions (average −35%, Fig. 3 and Supplementary Table 3). Interestingly, organisms from tropical regions were shown to be especially susceptible to global change throughout all ontogenetic stages, with HE (−38%), OA (−17%), OW (−28%) and OW + OA (−29%) all prompting inhibitory effects (Fig. 3 and Supplementary Table 3). This consistent pattern is potentially linked to physiological thresholds, since unlike temperate inhabitants, animals residing in currently warmer environments are generally already close to their maximum thermal thresholds (or have a narrower thermal window), which makes them more susceptible to further temperature increases[7,43], especially if coupled with effects from other stressors, such as OA[25,32]. Similarly, the higher vulnerability of earlier life stages (lower buffering capabilities and physiological tolerance) may explain the detrimental effects of OW + OA and OW on eggs/larvae of temperate animals, as well as the absence of negative effects on juveniles and adults from this climate region. Thus, while OA, OW and OW + OA effects on heterotrophs are more specific to tropical regions (and early stages in temperate regions), HE impacts are pervasive across climate regions and resistance to this stressor does not increase throughout an organism's lifespan.

Perspectives, caveats and future directions

HE impacts on the performance of marine organisms were greater than those of the other experimentally tested global change stressors, inhibiting all biological responses analysed across different categories. Rising temperatures (OW) can markedly shape physiological performance by inhibiting or stimulating biological traits, depending on where the changes start within the organism's physiological thermal window[7,43]. While less pronounced, increases in H^+ concentrations (OA) and reduced carbonate precipitation are linked to altered acid–base regulation and calcification processes[6,24]. Theoretically, by indirectly provoking shifts in energy allocation, or by directly increasing physiological (for example, oxidative) stress and lowering thermal/acid–base regulation limits, biological responses elicited by OW and OA could be exacerbated when both stressors co-occur[25,32]. Taking into account higher stressor size magnitudes relatively to isolated treatments (Supplementary Fig. 3 and Supplementary Table 4), in general the combination of OW + OA did not significantly increase effect sizes yielded by isolated stressors but did produce more pervasive negative effects, for example in the reproduction and development of marine animals.

Concurrently, as most animals have a primarily aerobic metabolism, accessibility to species-specific minimum required levels of dissolved O_2 content is critical[28,37]. Indeed, impoverishment of O_2 is known to trigger avoidance behaviour, constraints on thermal ranges and associated biogeography[22], deep physiological modifications and widespread mortality throughout food webs[16,17,28,44]. Thus, given the fundamental role of O_2 for (especially higher) life forms in the marine environment, HE causes strong inhibitory effects across all biological responses, taxonomical groups, climate regions and ontogenetic life stages of marine biota. It is important to note that we do not identify O_2 depletion per se to be more impactful than an 'equal' (as a ratio) increase in temperature or H^+ concentration. Here, we refer to increasing temperature and decreasing pH corresponding to IPCC projections for 2100, that is stressor sizes that are

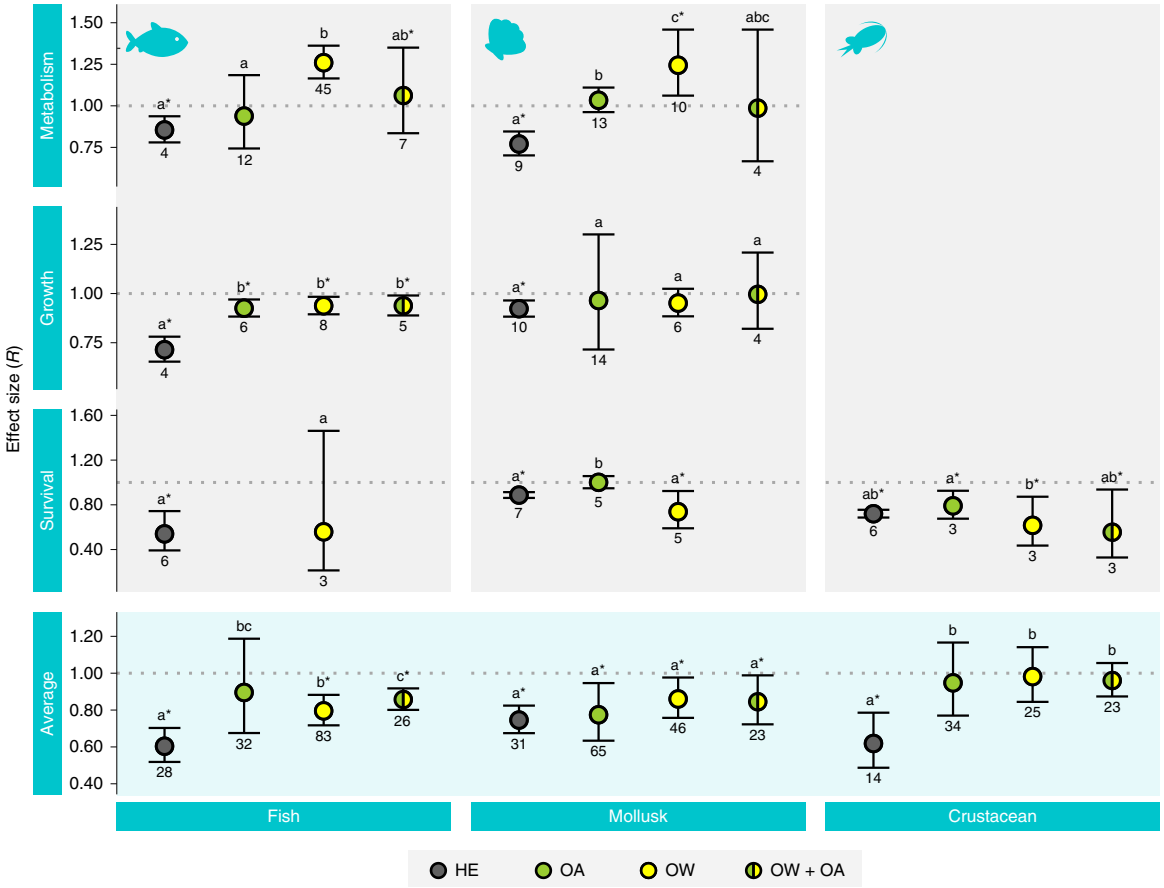

Fig. 2 | Average and detailed biological responses of the main heterotrophic taxonomic groups to global change stressors. Survival, metabolism and growth responses of crustaceans, mollusks and fish, to HE, OA, OW, and OW + OA, taking into account stressor size levels. Asterisks indicate significant effect sizes (HMMMs, 95% CI does not overlap $R = 1$), different letters show significant differences among stressors (Tukey HSD tests, $P < 0.05$) and numbers indicate sample sizes (number of experiments) for each effect size. Statistical outputs are available in Supplementary Table 2.

commonly designated as OW and OA, which have been the standard stressor metrics in the climate change research community for the last two decades[19,20,23].

The present meta-analysis identifies oxygen loss (HE) as a major anthropogenic-related stressor, posing a severe and pervasive risk to marine organisms and exceeding the combined effects projected for OW and OA. Our study also points to strong HE impacts on a wide range of biological responses, affecting marine life at different levels of organization, which can be expected to elicit cascading effects in marine ecosystems with potential socioeconomic ramifications[18]. Concordantly, an examination of biodiversity patterns across natural multistressor gradients in upwelling systems found that oxygen levels superseded temperature and CO_2 as explanatory factors for macroinvertebrate biodiversity trends in the Eastern Pacific[45]. Thus, given the already-known marked effects on several key ecological and biological features, for example identity and density of individual species, life-styles, reproductive success and larval development, feeding modes and biomass (this study and refs. [3,17,27–29]), HE will potentially elicit major changes in community structure and composition (both in terms of biodiversity and functioning) in future oceans. It is worth noting, however, that our analysis included few data on organisms adapted to extremely high levels of oxygen in the ocean (such as polar biota, only one study for HE) and organisms from oxygen minimum zones (OMZs) that have evolved to tolerate low O_2 conditions and may persist, if declining oxygen levels do not fall below their critical thresholds.

The prevalence and magnitude of HE impacts demonstrated across traits and taxa indicate that current global change-related research efforts should pay far more attention to the role of oxygen concentration as a stressor. The lack of studies using IPCC projections to address the biological impacts of (average) OD represents an important knowledge gap in climate change research. On the other hand, extreme phenomena, such as HE, MHW, and EAEs have the potential to be even more devastating than their long-term equivalents, as their sudden onset and transient nature deeply limit the potential for acclimation and adaptation of marine biota. Importantly, these phenomena are already taking place and have present-day consequences from both an ecological and a socioeconomic standpoint[11,17,46]. With these phenomena expected to become more widespread and to escalate in intensity over the next decades[3,4,33,46], it is of paramount importance to address them under controlled conditions, to better understand their consequences and ramifications. By mimicking and rescaling current-day events and incorporating regional trends and characteristics, experimental research should be able to provide solid grounds for science-based decision-making and informed risk assessments[10].

Due to insufficient number of papers fitting the criteria, the combined effects of HE with other stressors could not be calculated in the present study. However, it is known that increasing temperature directly and indirectly diminishes O_2 content[13] and that decreasing pH (or elevated CO_2) is also correlated with O_2-poor conditions through organic matter degradation and increased respiration[4,33,37]. For instance in OMZs, where hypoxic waters are usually rich in CO_2 and relatively cold, critical oxygen thresholds of animals tend to be low, thus promoting survival of adapted fauna[47]. More recently, studies focusing on the combined impacts of extreme levels of low

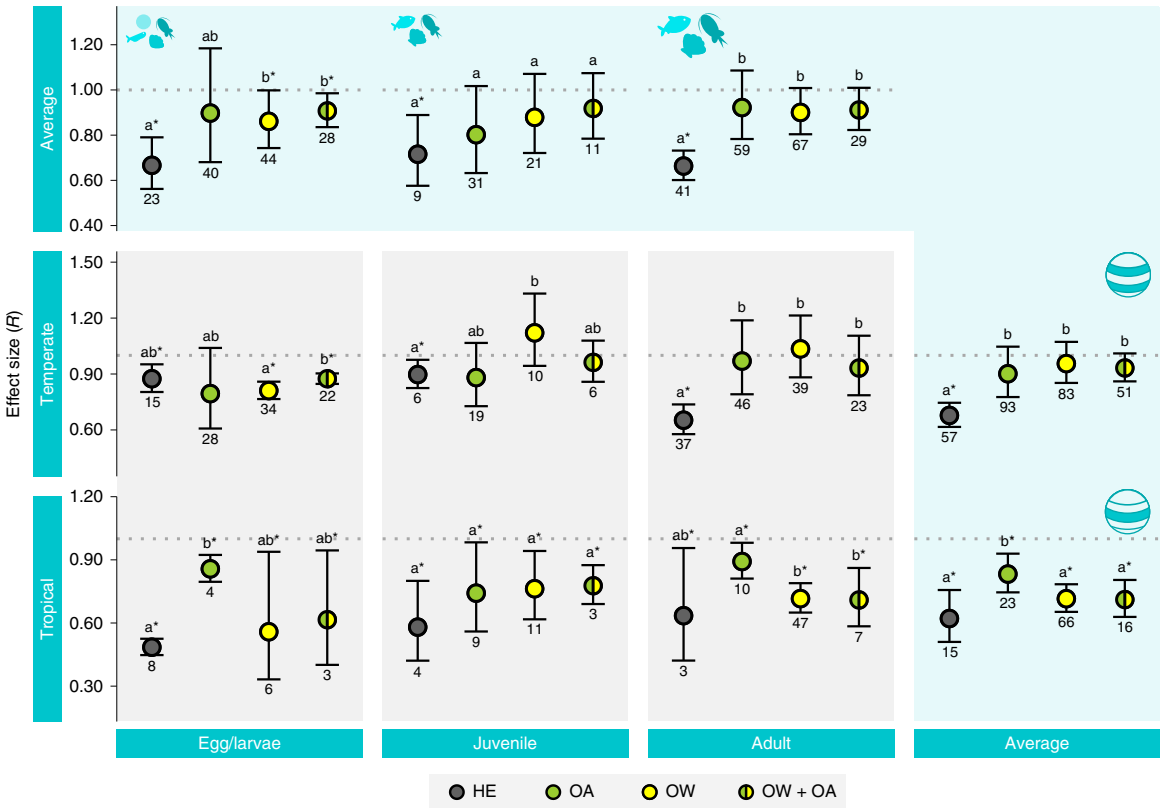

Fig. 3 | Average biological responses across ontogenetic life stages and/or climate regions of the main heterotrophic taxonomic groups to global change stressors. Average (all biological responses) response over egg/larva, juvenile and adult life stages, as well as temperate and subtropical/tropical regions, of the main taxonomic groups (that is, combining crustaceans, mollusks, and fish) to HE, OA, OW, and OW + OA, taking into account stressor size levels. Asterisks indicate significant effect sizes (HMMMs, 95% CI does not overlap R=1), different letters show significant differences among stressors (Tukey HSD tests, P<0.05) and numbers indicate sample sizes (number of experiments) for each effect size. Statistical outputs available in Supplementary Table 3.

O_2 and high CO_2 have found primarily additive negative impacts on marine animals[48–50]. Similarly, large scale changes in temperature and O_2 are reported to jointly lower physiological thresholds in marine biota[37]. In accordance, metabolic-based projections for the future indicate that increasing temperatures and associated decreases in dissolved O_2 content will considerably constrain animal habitat under climate change[51].

Yet, experimental studies gauging the joint impact of all three stressors on marine fauna are still scarce, leaving a gap for the scientific community to fill. For instance, a rare study assessing the combined OW, OA and HE impacts on abalone, showed that HE and OA prompted an even stronger narrowing of thermal tolerance range than HE alone[52], suggesting further exacerbation of pairwise-generated negative impacts. Building on the previously mentioned projection models and physiological mechanisms, past records indicate that extreme levels of the deadly trio jointly contributed to mass extinction events, where approximately 95% of all marine species became extinct, for example the Great Permian Extinction[53,54]. As such, studies addressing the interplay between all three elements of the deadly trio in a balanced design, aiming to assess the impacts of gradual but perhaps more urgently, extreme and sudden changes, represent high-ranking priorities in the field. It is paramount to move towards multistressor scenarios (for example, ref. [36]) that incorporate oxygen depletion, to generate more holistic and accurate predictions of biological responses to the oceans of tomorrow.

Methods

Meta-analysis design. *Defining stressor criteria.* Stressor manipulation levels for OA and OW were based on the widely used and well-established projections set by the IPCC for 2100 OA and OW[1]. The 'business-as-usual' scenario (RCP 8.5) served as reference for these stressors, since: (1) nearly 30 years after the first definition of global change scenarios, greenhouse gas emissions (and consequent climate alterations) are yet to deviate from predictions and more optimistic scenarios are not backed by current trends[1,55]; (2) a delta pH equal or inferior to −0.4 (which translates to a p_{CO_2} delta of ~500 ppm), or a temperature delta equal or inferior to +4 °C (Supplementary Data 1) represent the most common levels of temperature and pH variation experimentally tested in the last 10–20 yr in the climate change research community[11,25].

As for HE, most O_2 experiments performed have not aimed to compare a concentration delta and usually target directly measured hypoxia (low O_2 concentrations) effects per se. Thus, our definition of HE is not given as a delta (as is the case for OW and OA) but rather as a comprehensive range of oxygen concentrations which usually characterize HE (1 and 3.5 O_2 mg l^{-1}), averaged around what is generally defined as hypoxia in coastal and shelf settings: ~2 O_2 mg l^{-1} (refs. [1,3,13,28,44]). We excluded oxygen treatment concentrations <1 mg l^{-1} (extreme hypoxic conditions in coastal systems), since these values are often lethal for marine taxa (see Fig. 3 in ref. [27]), or >3.5 mg l^{-1}, which defines limitations for the most active fishes[28]. Simultaneously, suitable controls were inherently defined as being acclimated to >3.5 mg l^{-1}, to provide a comparable control–treatment response (lowest O_2 concentration used for control conditions was 5 mg l^{-1}; Supplementary Data 2). Consequently, species fully adapted to oxygen-poor conditions, for example inhabitants of the Eastern Pacific and Indian Ocean oxygen-limiting and OMZs (sensu ref. [56]), were automatically excluded. A relatively high upper limit for O_2 hypoxic concentrations (3.5 mg l^{-1}) was used[28], yielding conservative results that do not focus on extreme changes in dissolved O_2 levels. To ensure better comparability to other stressor effects, we incorporated an O_2 delta, primarily using explicitly stated control O_2 concentrations within research papers, or retrieving mean oxygen concentrations for the paper's geographic location and year, from datasets made available upon request from the National Ocean and Atmospheric Administration (NOAA) World Ocean Database[57].

In terms of direct stressor comparison, while the most fitting framework would be to likewise estimate O_2 loss impacts using OD projections for 2100 (5–10% loss of O_2, refs. [12,13]), the marked scarcity of experimental data testing very small O_2 differences precludes that approach. It is worth noting that the experimental procedures aiming to emulate OW and OA projections for 2100 (RCP 8.5) closely resemble the conditions of present-day strong/severe MHWs[46] and EAEs[26,58]

both in terms of stressor change range (most MHWs average below +4 °C during their span[46] and EAEs where a 0.4 pH drop is maintained throughout are also infrequent[15,59]) and particularly exposure period (average ~43 d of experimental exposure for OW, OA and OW + OA; Supplementary Data 2). In this context, the rejection of studies featuring extreme hypoxia concentrations further improves stressor comparability. Moreover, given that more extreme levels of OW and OA still occur in nature, we statistically compensated for differences in stressor size manipulations within and among stressors, by incorporating these stressor sizes in the HMMM analyses and computing effect sizes dependent on the degree of stressor manipulation (see Statistical analyses).

Literature search. Using Google Scholar and ISI Web of Knowledge, the available literature was scrutinized for experimental/manipulative papers that gauged the effects of global change-related environmental stressors (warming, acidification, and hypoxia) on biological responses of coastal marine biota (for example, survival, abundance, growth, metabolism, reproduction and development). We used the keywords 'warming', 'acidification' and 'hypoxia', in pairwise combinations, together with 'ocean', 'sea' or 'marine' (for example, acidification AND warming AND ocean; acidification AND hypoxia AND sea) completing nine searches. Given the low number of papers yielded for 'hypoxia', we performed an additional search, for which keywords included this stressor alone and the words 'ocean', 'sea' or 'marine' alternately (three more searches, total of 12). Papers published between 1 January 1990 (roughly marking the emergence of experimental studies directly assessing the effects of global change in marine biota; Supplementary Fig. 1) and 1 March 2016 (end of search) were considered, yielding an initial pool of ~700 papers and ~2,000 experiments (Supplementary Data 1).

Not considered were papers where quantitative stressor values were missing ($n = 8$), controls were not suitable (presence of other confounding factors, for example different levels of light, unstable parameters; $n = 43$), pH was changed using acid addition ($n = 6$) and any form of data variation (standard deviation, standard error, confidence intervals or variance; $n = 34$) or sample size (absence or pseudoreplication; $n = 30$) was not reported or possible to determine (Supplementary Data 1). From the initially selected papers and experiments (Supplementary Data 1), inclusion/exclusion criteria yielded 136 papers, corresponding to 721 different control–treatment comparisons, that is experiments (Supplementary Data 2)[32,39–42,58,60–189]. For a detailed description of the number of papers removed at each step of the process, see the flow diagram elaborated following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Fig. 2) and Supplementary Data 1 for the specific rejection criteria used case-by-case. We took into consideration the PRISMA checklist for meta-analysis and review papers/experiments to ensure the best practice in reporting meta-analyses[190].

Data collection. Datapoints, error estimates and sample sizes were retrieved from tables or calculated from figures using freely available graphical software (Im2graph, v.1.20). Error estimates in papers (variance, standard deviation, 95% confidence intervals or standard errors) were transformed to standard error before inclusion in meta-analysis, through appropriate mathematical formulas using sample sizes and means. Whenever the nature of error estimates was unreported, either on the manuscript or supplemental data, we searched online on data repositories for said information (for example, OA-ICC, PANGAEA). When valid information about the nature of error was still not retrieved, the paper would be removed from analysis, according to the aforementioned rejection criteria (variation not reported/could not calculate response ratio). In cases where control treatments showed no variance (for example, some experiments report 100% survival under control conditions), we used the variance reported in the stressor treatment for controls as well, to make calculations possible and conservative. If data were presented as log-transformed, we performed a reverse transformation (antilog) before definite inclusion in the dataset.

The low number of papers that assessed combined stressor impacts HE + OA ($n = 1$) and HE + OW ($n = 2$) (Supplementary Data 1), precluded the calculation of effect sizes for these interactions and thus only the interaction OW + OA was considered for HMMMs analyses. When multiple levels of a stressor (for example, OW) were tested and described in a paper/experiment, only the closest to the designated maximum delta (for example, $\Delta T = +4$ °C) was taken as the treatment level. In multispecies papers/experiments (for example, multiple species in the same mesocosm), responses from distinct species were collected separately, even though their responses were not completely independent. Here, we followed the reasoning of previous meta-analyses papers, which state that non-independent indirect effects of acidification, warming and hypoxia such as species interactions are relevant to future scenarios of climate (or global) change, where species will be impacted by both direct and indirect effects[8,24,25]. Moreover, this issue was also addressed statistically by the introduction of random effects in the meta-analysis models (see below).

Data on different biological responses to stressors were collected, including: survival, abundance, metabolism, growth, development, reproduction, behaviour, bleaching, photosynthesis, calcification and enzymatic rates. In papers/experiments where the same biological response was gauged several times through different metrics (for example, growth measured as changes in biomass, length and width), only the most biologically inclusive metric was considered (for example, biomass instead of length for estimating growth) to avoid pseudoreplication[25,34]. As such, survival was typically reported as the percentage or number of individuals alive, at the end of the experiment. Papers assessing abundance responses were more common in the field and were defined as the number of individuals (including number of newly settled individuals). Metabolism was primarily taken as changes in metabolic measurements, such as aerobic scope or maximum metabolic rates. Development was mainly assessed through number of individuals successfully developing over ontogenetic stages. Reproduction was measured through number of eggs produced or quantification of sexual hormones. Changes in behavioural processes (behaviour), number of *Symbiodinium* cells (bleaching), calcium carbonate concentration (calcification), stress-driven changes in antioxidant enzymes (enzymatic rates) and photosynthetic rates (photosynthesis) were also registered. Biological responses with fewer than three datapoints ($n = 3$) were not isolated for analyses. Thus, after a first general analysis (Supplementary Table 1), we trimmed responses to include only those with sufficient data to calculate related impacts (for example, survival, abundance, metabolism, growth, development and reproduction; Fig. 1).

Data were organized by three stressors and one stressor combination (four stressor levels), namely: HE, OW, OA and combined OW + OA. Beyond biological responses, we hierarchically subdivided data into subsets within: (1) taxonomical groups (fish, mollusk, crustacean, echinoderm and coral), from which fish, mollusk and crustacean were considered as the main taxonomical representatives of heterotrophs; (2) climate region where the organisms reside (temperate or tropical/subtropical); and (3) ontogenetic life stage (egg/larva, juvenile and adult).

Statistical analyses. *Hierarchical mixed-effects models.* Meta-analyses were performed on R software[191], using the function rma.mv (meta-analysis via multivariate/multilevel linear mixed-effects models) available in the metafor package[192,193] (see Supplementary Data 3 for the R Script used). First, to calculate effect size and variance estimates for each of the control–treatment comparisons, we used the function escalc, introducing:

dat = escalc(m1i = M_T, sd1i = SD_T, n1i = N_T, m2i = M_C, sd2i = SD_C, n2i = N_C, measure = "ROM", data = DataS2, append = TRUE) (see Supplementary Data 3).

'ROM' calculates the ln-transformed response ratio (lnR; ref. [35]) between controls and treatment, as lnR = ln(M_T/M_C), while variance for each comparison is calculated as: variance = $SD\_T^2/(N\_T * M\_T^2) + SD\_C^2/(N\_C * M\_C^2)$. Afterwards, we fitted the meta-analytic multivariate hierarchical mixed-effects models (see Supplementary Data 3 for more examples), using the function rma.mv:

model = rma.mv(ln*R*, variance, method = "REML", test = "t", random = list (~Stressor | Experiment, ~Paper | Experiment), struct = "UN", mods = ~lnSR : Stressor – 1, data = dat).

The inclusion of '–1' for the categorical moderator (Stressor) calculates estimates for each of the levels within said moderator, contrasted with a dummy variable zero (directly testing the null hypothesis), instead of using one of the moderator levels as a reference baseline. Only the interaction term between moderators was used, since models with this structure consistently reported the lowest Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC) values. We included a second moderator, the natural logarithm of the ratio between control and treatment levels for each experiment (written as 'lnSR', Supplementary Data 2 and Supplementary Data 3), interacting with the Stressor moderator (calculated as ln*R*), to take into account stressor manipulation levels and proportionally calculate effect sizes. For HE, we calculated stressor size as the natural logarithm of the ratio between O_2 concentrations at the control and treatment conditions. For OA, since pH is already a logarithmic scale, we transformed to the natural logarithm and retained the difference between control and treatment pH levels. Since temperature scaling is highly variable, we used 2 °C, that is the absolute value corresponding to the freezing point of seawater (–2 °C), as a reference baseline and computed the ratio between control and treatment (for example, +4 °C) conditions. Stressor size values for OW + OA treatment were obtained by summing the respective ratios of OW and OA. We used generalized linear mixed modelling with a similar structure to the HMM, to describe the relationship between stressor size and effect size (Supplementary Fig. 3 and Supplementary Table 4). Models were posteriorly validated, by checking for normality in residuals, homogeneity of variances, homoscedasticity and leverage (Supplementary Data 3). All stressor size values are available in Supplementary Data 2 (lnSR).

We included two random effects, 'Stressor | Experiment' and 'Paper | Experiment', to independently calculate intercepts and slopes within levels, minimizing (multi)collinearity; for example, in experiments from the same paper and experiments where several stressors were measured. We extended independency within models as much as possible, by using structures that maximized heterogeneity calculation, allowing for level-specific (instead of estimating one value for all levels), independent computation of effect sizes and correlations values, between and within the levels of the inner and outer components of both random effects (see more in ref. [193] and https://cran.r-project.org/web/packages/metafor/metafor.pdf). Thus, we attempted to model data starting from the highest complexity structure and gradually decreased according

to the following order (according to rma.mv and metafor documentation): unstructured variance/covariance matrix ('UN'), heteroscedastic compound symmetry ('HCS'), diagonal matrix ('DIAG'), compound symmetry ('CS') and scaled identity-matrix ('ID'). Thus, we began with a completely unstructured variance/covariance matrix where all parameters were calculated case-by-case ('UN'), to a structure ('ID') where within and between-level correlation coefficients were set to 0 (see more in ref. [193]). Most of our models were run with either 'UN' or 'HCS' structure (Supplementary Data 3), thus entailing high independency between stressors, papers and experiments.

Lastly, to verify significance of effect sizes and confidence intervals calculated using restricted maximum likelihood, instead of using the default z-statistic (k degrees of freedom), we performed t-tests. Since t-statistics resort to a t-distribution with $k-p$ degrees (where p is the total number of model coefficients), they provide more conservative results for small sample sizes, that is larger standard errors are computed to deal with uncertainty[193,194].

Testing differential stressor impacts and analysed subdatasets. Use of the same HMMM to calculate effect sizes and 95% CI estimates for each level within a moderator, enabled us to find significant differences between levels (for example, H versus OA), in a pairwise post hoc analysis[34,195]. To formally test for differences among levels of each moderator within the mixed-model, we applied Tukey's honest significance tests (package multcomp) using general linear hypotheses (command ghlt) and creating a contrast matrix between all stressor levels using contrMat (Supplementary Data 3).

In a step by step approach and always incorporating Stressor Size as an interactive moderator, we undertook a hierarchical design, performing several sequential mixed-effects models to test the effect of moderators, that is variables with potential to influence the response of marine biota to stressor impact (distinct stressors, response variable, taxonomical groups, climate region and life stage). We first assessed the mean effect of each stressor (HE, OW, OA and OW + OA), irrespective of biological responses (including behaviour, bleaching and calcification) (Supplementary Table 1). We then created subsets of those data and individual models were computed assessing the effect of stressors for each biological response (Fig. 1). Within those subsets, we further analysed differences in stressor impacts within the three main animal taxonomic groups (Fig. 2 and Supplementary Table 2). Lastly, after taking the negative symmetric value for metabolism and feeding (to prevent counterdirectional effect sizes), a final analysis was performed which gauged stressor effects on these three taxonomic groups, according to ontogenetic life stage and climate region (Fig. 3 and Supplementary Table 3). See Supplementary Tables for model results summarized according to estimates for each stressor and Supplementary Data 3 for full model structures and results, as well as (sub)datasets used (Supplementary Data 2 as well).

After concluding analyses, lnR and 95% CI estimates were back transformed to R (ref. [34]). We used the antilog (exponential function) to remove the natural logarithm and allow for a better biological interpretation of the yielded results[34,35]. R is interpreted similarly to ln$R$, except that the reference value (where control = treatment) to which R is (non-)significant is 1. Therefore, values where $R > 1$ show a stimulation of the variable, while $R < 1$ represents an inhibition of the variable.

Publication bias. To assess the robustness of observed effects, we carried out several analyses to detect: (1) the observable presence of bias (observation of funnel plots), (2) artefacts stemming from unseen bias (Rosenthal's fail-safe number) and (3) how much impact a potential bias could have (Duval and Tweedie's Trim and Fill)[34]. The Rosenthal's fail-safe number (N_{fs}) determines the number of effect sizes with no significant effect that are needed to change the significance (P value) reported by the model. Defined as $5n + 10$ (where n was the number of experiments), the N_{fs} was above the threshold in all cases reported. Importantly, all Trim and Fill operations that reported a correction of mean estimates and CIs, did so by increasing the magnitude of the effect. Given that CIs of the main analysis and the Trim and Fill analysis still overlapped, we opted to report the results from the main analysis, which were therefore more conservative (see Supplementary Data 3 for case-by-case differences).

Sensitivity analyses. Using forest plots, the disproportionate contribution of an experiment with a large magnitude effect size to a specific result was assessed by ranking each individual experiment by the magnitude of its effect size, followed by a one-at-a-time removal of the experiments with the largest magnitude effect sizes and re-running the analyses (Supplementary Data 3). If the exclusion of a specific experiment changed the significance of the overall mean effect size or the heterogeneity statistic, these analyses would be re-run excluding that specific experiment. The same rationale was applied at a paper level, that is papers contributing more than five experiments were removed and the analysis was re-run to determine if statistical significance changed due to that particular paper. Lastly, as we collected several datapoints from one paper, for example biological responses such as survival and metabolism, we performed an extra step to minimize non-independence issues in the hierarchical mixed-effects approach and checked for paper bias on the amount of experiments retrieved. To the lowest hierarchical level possible (when number of papers = 3), all analyses were recalculated with a single effect size for each stressor per paper, which was calculated via a mixed-effects model as the weighted mean effect size of all combined experiments (for example, different biological responses) from that paper[34] (Supplementary Data 3).

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

Data availability

All data relating to this manuscript are available in Supplementary Data files.

Code availability

All code relating to this manuscript are available in Supplementary Data files.

Received: 12 February 2020; Accepted: 1 December 2020;
Published online: 11 January 2021

References

1. IPCC *Climate Change 2013: The Physical Science Basis* (eds Stocker, T. F. et al.) (Cambridge Univ. Press, 2013).
2. Laffoley, D. & Baxter, J. M. *Ocean Deoxygenation: Everyone's Problem—Causes, Impacts, Consequences and Solutions* (IUCN, 2019).
3. Levin, L. A. Manifestation, drivers, and emergence of open ocean deoxygenation. *Ann. Rev. Mar. Sci.* **10**, 229–260 (2018).
4. Altieri, A. H. & Gedan, K. B. Climate change and dead zones. *Glob. Change Biol.* **21**, 1395–1406 (2015).
5. Bijma, J., Pörtner, H. O., Yesson, C. & Rogers, A. D. Climate change and the oceans—what does the future hold? *Mar. Pollut. Bull.* **74**, 495–505 (2013).
6. Wittmann, A. C. & Pörtner, H. O. Sensitivities of extant animal taxa to ocean acidification. *Nat. Clim. Change* **3**, 995–1001 (2013).
7. Pörtner, H. O. & Knust, R. Climate change affects marine fishes through the oxygen limitation of thermal tolerance. *Science* **315**, 95–98 (2007).
8. Nagelkerken, I. & Connell, S. D. Global alteration of ocean ecosystem functioning due to increasing human CO_2 emissions. *Proc. Natl Acad. Sci. USA* **112**, 13272–13277 (2015).
9. Frazão Santos, C. et al. Ocean planning in a changing climate. *Nat. Geosci.* **9**, 730 (2016).
10. Frazão Santos, C. et al. Integrating climate change in ocean planning. *Nat. Sustain.* **3**, 505–516 (2020).
11. IPCC *Climate Change 2014: Impacts, Adaptation, and Vulnerability* (eds Field, C. B. et al.) (Cambridge Univ. Press, 2014).
12. Bopp, L. et al. Multiple stressors of ocean ecosystems in the 21st century: projections with CMIP5 models. *Biogeosciences* **10**, 6225–6245 (2013).
13. Keeling, R. F., Körtzinger, A. & Gruber, N. Ocean deoxygenation in a warming world. *Ann. Rev. Mar. Sci.* **2**, 199–229 (2010).
14. Oliver, E. C. J. et al. Longer and more frequent marine heatwaves over the past century. *Nat. Commun.* **9**, 1324 (2018).
15. Burger, F. A., John, J. G. & Frölicher, T. L. Increase in ocean acidity variability and extremes under increasing atmospheric CO_2. *Biogeosciences* **17**, 4633–4662 (2020).
16. Diaz, R. J. & Rosenberg, R. Spreading dead zones and consequences for marine ecosystems. *Science* **321**, 926–929 (2008).
17. Breitburg, D. et al. Declining oxygen in the global ocean and coastal waters. *Science* **359**, eaam7240 (2018).
18. *Special Report on the Ocean and Cryosphere in a Changing Climate* (IPCC, 2019).
19. Sampaio, E. & Rosa, R. in *Climate Action. Encyclopedia of the UN Sustainable Development Goals* (eds Leal Filho, W. et al.) (Springer, 2019); https://doi.org/10.1007/978-3-319-71063-1_90-1
20. Wernberg, T., Smale, D. A. & Thomsen, M. S. A decade of climate change experiments on marine organisms: procedures, patterns and problems. *Glob. Change Biol.* **18**, 1491–1498 (2012).
21. Hooper, D. U. et al. A global synthesis reveals biodiversity loss as a major driver of ecosystem change. *Nature* **486**, 105–108 (2012).
22. Sunday, J. M., Bates, A. E. & Dulvy, N. K. Thermal tolerance and the global redistribution of animals. *Nat. Clim. Change* **2**, 686–690 (2012).
23. Poloczanska, E. S. et al. Global imprint of climate change on marine life. *Nat. Clim. Change* **3**, 919–925 (2013).
24. Kroeker, K. J., Kordas, R. L., Crim, R. N. & Singh, G. G. Meta-analysis reveals negative yet variable effects of ocean acidification on marine organisms. *Ecol. Lett.* **13**, 1419–1434 (2010).
25. Kroeker, K. J. et al. Impacts of ocean acidification on marine organisms: quantifying sensitivities and interaction with warming. *Glob. Change Biol.* **19**, 1884–1896 (2013).
26. Ng, C. A. & Micheli, F. Short-term effects of hypoxia are more important than effects of ocean acidification on grazing interactions with juvenile giant kelp (*Macrocystis pyrifera*). *Sci. Rep.* **10**, 5403 (2020).

27. Vaquer-Sunyer, R. & Duarte, C. M. Thresholds of hypoxia for marine biodiversity. *Proc. Natl Acad. Sci. USA* **105**, 15452–15457 (2008).
28. Stramma, L. et al. Expansion of oxygen minimum zones may reduce available habitat for tropical pelagic fishes. *Nat. Clim. Change* **2**, 33–37 (2012).
29. Diaz, R. et al. Marine benthic hypoxia: a review of its ecological effects and the behavioural responses of benthic macrofauna. *Oceanogr. Mar. Biol.* **33**, 246–303 (1995).
30. Levin, L. A. et al. Effects of natural and human-induced hypoxia on coastal benthos. *Biogeosciences* **6**, 2063–2098 (2009).
31. Sampaio, E. et al. Ocean acidification dampens physiological stress response to warming and contamination in a commercially-important fish (*Argyrosomus regius*). *Sci. Total Environ.* **618**, 388–398 (2018).
32. Rosa, R. & Seibel, B. A. Synergistic effects of climate-related variables suggest future physiological impairment in a top oceanic predator. *Proc. Natl Acad. Sci. USA* **105**, 20776–20780 (2008).
33. Klein, S. G., Steckbauer, A. & Duarte, C. M. Defining CO_2 and O_2 syndromes of marine biomes in the Anthropocene. *Glob. Change Biol.* **26**, 355–363 (2020).
34. Ferreira, V. et al. A meta-analysis of the effects of nutrient enrichment on litter decomposition in streams. *Biol. Rev.* **90**, 669–688 (2015).
35. Hedges, L. V., Gurevitch, J. & Curtis, P. S. The meta-analysis of response ratio in experimental ecology. *Ecology* **80**, 1150–1156 (1999).
36. Rillig, M. C. et al. The role of multiple global change factors in driving soil functions and microbial biodiversity. *Science* **366**, 886–890 (2019).
37. Vaquer-Sunyer, R. & Duarte, C. M. Temperature effects on oxygen thresholds for hypoxia in marine benthic organisms. *Glob. Change Biol.* **17**, 1788–1797 (2011).
38. Lemoine, N. P. & Burkepile, D. E. Temperature-induced mismatches between consumption and metabolism reduce consumer fitness. *Ecology* **93**, 2483–2489 (2012).
39. Schram, J., Schoenrock, K., McClintock, J., Amsler, C. & Angus, R. Seawater acidification more than warming presents a challenge for two Antarctic macroalgal-associated amphipods. *Mar. Ecol. Prog. Ser.* **554**, 81–97 (2016).
40. Rummer, J. L. et al. Life on the edge: thermal optima for aerobic scope of equatorial reef fishes are close to current day temperatures. *Glob. Change Biol.* **20**, 1055–1066 (2014).
41. Ferrari, M. C. O. et al. Interactive effects of ocean acidification and rising sea temperatures alter predation rate and predator selectivity in reef fish communities. *Glob. Change Biol.* **21**, 1848–1855 (2015).
42. Munday, P. L., Crawley, N. E. & Nilsson, G. E. Interacting effects of elevated temperature and ocean acidification on the aerobic performance of coral reef fishes. *Mar. Ecol. Prog. Ser.* **388**, 235–242 (2009).
43. Stillman, J. H. Acclimation capacity underlies susceptibility to climate change. *Science* **301**, 65 (2003).
44. Chan, F. et al. Emergence of anoxia in the California current large marine ecosystem. *Science* **319**, 920 (2008).
45. Sperling, E. A., Frieder, C. A. & Levin, L. A. Biodiversity response to natural gradients of multiple stressors on continental margins. *Proc. R. Soc. B* **283**, 20160637 (2016).
46. Hobday, A. J. et al. Categorizing and naming marine heatwaves. *Oceanography* **31**, 162–173 (2018).
47. Levin, L. A. & Bris, N. L. The deep ocean under climate change. *Science* **350**, 766–768 (2015).
48. Steckbauer, A., Klein, S. G. & Duarte, C. M. Additive impacts of deoxygenation and acidification threaten marine biota. *Glob. Change Biol.* **26**, 5602–5612 (2020).
49. Francis Chan, B., Barth, J. A., Kroeker, K. J., Lubchenco, J. & Menge, B. A. The dynamics and impact of ocean acidification and hypoxia. *Oceanography* **32**, 62–71 (2019).
50. Tomasetti, S. J. & Gobler, C. J. Dissolved oxygen and pH criteria leave fisheries at risk. *Science* **368**, 372–373 (2020).
51. Deutsch, C., Ferrel, A., Seibel, B., Pörtner, H.-O. & Huey, R. B. Climate change tightens a metabolic constraint on marine habitats. *Science* **348**, 6239 (2015).
52. Tripp-Valdez, M. A. et al. Metabolic response and thermal tolerance of green abalone juveniles (*Haliotis fulgens*: Gastropoda) under acute hypoxia and hypercapnia. *J. Exp. Mar. Biol. Ecol.* **497**, 11–18 (2017).
53. Benton, M. J. & Twitchett, R. J. How to kill (almost) all life: the end-Permian extinction event. *Trends Ecol. Evol.* **18**, 358–365 (2003).
54. Penn, J. L., Deutsch, C., Payne, J. L. & Sperling, E. A. Temperature-dependent hypoxia explains biogeography and severity of end-Permian marine mass extinction. *Science* **362**, eeaat1327 (2018).
55. IPCC *Global Warming of 1.5 °C* (eds Masson-Delmotte, V. et al.) (WMO, 2018).
56. Gilly, W. F., Beman, J. M., Litvin, S. Y. & Robison, B. H. Oceanographic and biological effects of shoaling of the oxygen minimum zone. *Ann. Rev. Mar. Sci.* **5**, 393–420 (2013).
57. Boyer, T. P. et al. *World Ocean Database 2018* NOAA Atlas NESDIS 87 (ed. Mishonov, A. V.) (NOAA, 2018); https://www.ncei.noaa.gov/products/world-ocean-database
58. Gobler, C. J., DePasquale, E. L., Griffith, A. W. & Baumann, H. Hypoxia and acidification have additive and synergistic negative effects on the growth, survival, and metamorphosis of early life stage bivalves. *PLoS ONE* **9**, e83648 (2014).
59. Hofmann, G. E. et al. High-frequency dynamics of ocean pH: a multi-ecosystem comparison. *PLoS ONE* **6**, e28983 (2011).
60. Basso, L., Hendriks, I., Steckbauer, A. & Duarte, C. Resistance of juveniles of the Mediterranean pen shell (*Pinna nobilis*) to hypoxia and interaction with warming. *Estuar. Coast. Shelf Sci.* **165**, 199–203 (2015).
61. Calder-Potts, R., Spicer, J. I., Calosi, P., Findlay, H. S. & Widdicombe, S. A mesocosm study investigating the effects of hypoxia and population density on respiration and reproductive biology in the brittlestar *Amphiura filiformis*. *Mar. Ecol. Prog. Ser.* **534**, 135–147 (2015).
62. Cheng, B. S. et al. Testing local and global stressor impacts on a coastal foundation species using an ecologically realistic framework. *Glob. Change Biol.* **21**, 2488–2499 (2015).
63. Couturier, C. S., Stecyk, J. A. W., Rummer, J. L., Munday, P. L. & Nilsson, G. E. Species-specific effects of near-future CO_2 on the respiratory performance of two tropical prey fish and their predator. *Comp. Biochem. Physiol. A* **166**, 482–489 (2013).
64. Pérez-López, P. et al. Life cycle assessment of the production of the red antioxidant carotenoid astaxanthin by microalgae: from lab to pilot scale. *J. Clean. Prod.* **64**, 332–344 (2014).
65. Garcia, R. N. et al. Interactive effects of mosquito control insecticide toxicity, hypoxia, and increased carbon dioxide on larval and juvenile Eastern oysters and hard clams. *Arch. Environ. Contam. Toxicol.* **66**, 450–462 (2014).
66. Lefevre, S., Watson, S.-A., Munday, P. L. & Nilsson, G. E. Will jumping snails prevail? Influence of near-future CO_2, temperature and hypoxia on respiratory performance in the tropical conch *Gibberulus gibberulus gibbosus*. *J. Exp. Biol.* **218**, 2991–3001 (2015).
67. Li, A. & Chiu, J. M. Y. Latent effects of hypoxia on the gastropod *Crepidula onyx*. *Mar. Ecol. Prog. Ser.* **480**, 145–154 (2013).
68. Rosa, R. et al. Lower hypoxia thresholds of cuttlefish early life stages living in a warm acidified ocean. *Proc. Biol. Sci.* **280**, 20131695 (2013).
69. Rosa, R., Gonzalez, L., Dierssen, H. M. & Seibel, B. A. Environmental determinants of latitudinal size-trends in cephalopods. *Mar. Ecol. Prog. Ser.* **464**, 153–165 (2012).
70. Styf, H. K., Nilsson Sköld, H. & Eriksson, S. P. Embryonic response to long-term exposure of the marine crustacean *Nephrops norvegicus* to ocean acidification and elevated temperature. *Ecol. Evol.* **3**, 5055–5065 (2013).
71. Sui, Y., Hu, M., Huang, X., Wang, Y. & Lu, W. Anti-predatory responses of the thick shell mussel *Mytilus coruscus* exposed to seawater acidification and hypoxia. *Mar. Environ. Res.* **109**, 159–167 (2015).
72. Thomsen, J., Casties, I., Pansch, C., Körtzinger, A. & Melzner, F. Food availability outweighs ocean acidification effects in juvenile *Mytilus edulis*: laboratory and field experiments. *Glob. Change Biol.* **19**, 1017–1027 (2013).
73. Vasquez, M. C., Murillo, A., Brockmann, H. J. & Julian, D. Multiple-stressor interactions influence embryo development rate in the American horseshoe crab, *Limulus polyphemus*. *J. Exp. Biol.* **218**, 2355–2364 (2015).
74. Donelson, J. M., Munday, P. L., Mccormick, M. I. & Nilsson, G. E. Acclimation to predicted ocean warming through developmental plasticity in a tropical reef fish. *Glob. Change Biol.* **17**, 1712–1719 (2011).
75. Gardiner, N. M., Munday, P. L. & Nilsson, G. E. Counter-gradient variation in respiratory performance of coral reef fishes at elevated temperatures. *PLoS ONE* **5**, e13299 (2010).
76. DePasquale, E., Baumann, H. & Gobler, C. J. Vulnerability of early life stage Northwest Atlantic forage fish to ocean acidification and low oxygen. *Mar. Ecol. Prog. Ser.* **523**, 145–156 (2015).
77. Hughes, B. B. et al. Climate mediates hypoxic stress on fish diversity and nursery function at the land–sea interface. *Proc. Natl Acad. Sci. USA* **112**, 8025–8030 (2015).
78. Lefevre, S., Damsgaard, C., Pascale, D. R., Nilsson, G. E. & Stecyk, J. A. W. Air breathing in the Arctic: influence of temperature, hypoxia, activity and restricted air access on respiratory physiology of the Alaska blackfish *Dallia pectoralis*. *J. Exp. Biol.* **217**, 4387–4398 (2014).
79. Lopes, A. R. et al. Oxidative stress in deep scattering layers: heat shock response and antioxidant enzymes activities of myctophid fishes thriving in oxygen minimum zones. *Deep. Res. Part I Oceanogr. Res. Pap.* **82**, 10–16 (2013).
80. Maas, A. E., Wishner, K. F. & Seibel, B. A. Metabolic suppression in thecosomatous pteropods as an effect of low temperature and hypoxia in the eastern tropical North Pacific. *Mar. Biol.* **159**, 1955–1967 (2012).
81. Penghan, L. Y., Cao, Z. D. & Fu, S. J. Effect of temperature and dissolved oxygen on swimming performance in crucian carp. *Aquat. Biol.* **21**, 57–65 (2014).

82. Sørensen, C., Munday, P. L. & Nilsson, G. E. Aerobic vs. anaerobic scope: sibling species of fish indicate that temperature dependence of hypoxia tolerance can predict future survival. *Glob. Change Biol.* **20**, 724–729 (2014).
83. Zittier, Z. M. C., Bock, C., Lannig, G. & Pörtner, H. O. Impact of ocean acidification on thermal tolerance and acid–base regulation of *Mytilus edulis* (L.) from the North Sea. *J. Exp. Mar. Biol. Ecol.* **473**, 16–25 (2015).
84. Zittier, Z. M. C., Hirse, T. & Pörtner, H.-O. The synergistic effects of increasing temperature and CO_2 levels on activity capacity and acid–base balance in the spider crab, *Hyas araneus*. *Mar. Biol.* **160**, 2049–2062 (2013).
85. Zhang, H., Shin, P. K. S. & Cheung, S. G. Physiological responses and scope for growth upon medium-term exposure to the combined effects of ocean acidification and temperature in a subtidal scavenger *Nassarius conoidalis*. *Mar. Environ. Res.* **106**, 51–60 (2015).
86. Wood, H. L., Spicer, J. I., Kendall, M. A., Lowe, D. M. & Widdicombe, S. Ocean warming and acidification; implications for the Arctic brittlestar *Ophiocten sericeum*. *Polar Biol.* **34**, 1033–1044 (2011).
87. Wolfe, K., Smith, A. M., Trimby, P. & Byrne, M. Vulnerability of the paper nautilus (*Argonauta nodosa*) shell to a climate-change ocean: potential for extinction by dissolution. *Biol. Bull.* **223**, 236–244 (2012).
88. Walther, K., Sartoris, F. J. & Pörtner, H. O. Impacts of temperature and acidification on larval calcium incorporation of the spider crab *Hyas araneus* from different latitudes (54° vs. 79°N). *Mar. Biol.* **158**, 2043–2053 (2011).
89. Walther, K., Anger, K. & Pörtner, H. O. Effects of ocean acidification and warming on the larval development of the spider crab *Hyas araneus* from different latitudes (54° vs. 79° N). *Mar. Ecol. Prog. Ser.* **417**, 159–170 (2010).
90. Vehmaa, A. et al. Projected marine climate change: effects on copepod oxidative status and reproduction. *Ecol. Evol.* **3**, 4548–4557 (2013).
91. Vehmaa, A., Brutemark, A. & Engström-Öst, J. Maternal effects may act as an adaptation mechanism for copepods facing pH and temperature changes. *PLoS ONE* **7**, e48538 (2012).
92. Uthicke, S. et al. Impacts of ocean acidification on early life-history stages and settlement of the coral-eating sea star *Acanthaster planci*. *PLoS ONE* **8**, e82938 (2013).
93. Towle, E. K., Enochs, I. C. & Langdon, C. Threatened Caribbean coral is able to mitigate the adverse effects of ocean acidification on calcification by increasing feeding rate. *PLoS ONE* **10**, e0123394 (2015).
94. Stubler, A. D., Furman, B. T. & Peterson, B. J. Sponge erosion under acidification and warming scenarios: differential impacts on living and dead coral. *Glob. Change Biol.* **21**, 4006–4020 (2015).
95. Small, D. P., Calosi, P., Boothroyd, D., Widdicombe, S. & Spicer, J. I. Stage-specific changes in physiological and life-history responses to elevated temperature and Pco_2 during the larval development of the European lobster *Homarus gammarus* (L.). *Physiol. Biochem. Zool.* **88**, 494–507 (2015).
96. Mackenzie, C. L., Lynch, S. A., Culloty, S. C. & Malham, S. K. Future oceanic warming and acidification alter immune response and disease status in a commercial shellfish species, *Mytilus edulis* L. *PLoS ONE* **9**, e0099712 (2014).
97. Schram, J. B., Schoenrock, K. M., McClintock, J. B., Amsler, C. D. & Angus, R. A. Multiple stressor effects of near-future elevated seawater temperature and decreased pH on righting and escape behaviors of two common Antarctic gastropods. *J. Exp. Mar. Biol. Ecol.* **457**, 90–96 (2014).
98. Schoepf, V. et al. Coral energy reserves and calcification in a high-CO_2 world at two temperatures. *PLoS ONE* **8**, e75049 (2013).
99. Di Santo, V. Ocean acidification exacerbates the impacts of global warming on embryonic little skate, *Leucoraja erinacea* (Mitchill). *J. Exp. Mar. Biol. Ecol.* **463**, 72–78 (2015).
100. Russell, B. D. et al. Ocean acidification and rising temperatures may increase biofilm primary productivity but decrease grazer consumption. *Philos. Trans. R. Soc. B* **368**, 20120438 (2013).
101. Rosa, R. et al. Differential impacts of ocean acidification and warming on winter and summer progeny of a coastal squid (*Loligo vulgaris*). *J. Exp. Biol.* **217**, 518–525 (2014).
102. Reyes-Nivia, C., Diaz-Pulido, G., Kline, D., Guldberg, O. H. & Dove, S. Ocean acidification and warming scenarios increase microbioerosion of coral skeletons. *Glob. Change Biol.* **19**, 1919–1929 (2013).
103. Putnam, H. M. & Gates, R. D. Preconditioning in the reef-building coral *Pocillopora damicornis* and the potential for trans-generational acclimatization in coral larvae under future climate change conditions. *J. Exp. Biol.* **218**, 2365–2372 (2015).
104. Poore, A. G. B. et al. Direct and indirect effects of ocean acidification and warming on a marine plant–herbivore interaction. *Oecologia* **173**, 111311–111324 (2013).
105. Pistevos, J. C. A., Nagelkerken, I., Rossi, T., Olmos, M. & Connell, S. D. Ocean acidification and global warming impair shark hunting behaviour and growth. *Sci. Rep.* **5**, 16293 (2015).
106. Pimentel, M. S. et al. Oxidative stress and digestive enzyme activity of flatfish larvae in a changing ocean. *PLoS ONE* **10**, e0134082 (2015).
107. Pimentel, M. S. et al. Defective skeletogenesis and oversized otoliths in fish early stages in a changing ocean. *J. Exp. Biol.* **217**, 2062–2070 (2014).
108. Pecorino, D., Barker, M. F., Dworjanyn, S. A., Byrne, M. & Lamare, M. D. Impacts of near future sea surface pH and temperature conditions on fertilisation and embryonic development in *Centrostephanus rodgersii* from northern New Zealand and northern New South Wales, Australia. *Mar. Biol.* **161**, 101–110 (2014).
109. Pansch, C., Nasrolahi, A., Appelhans, Y. S. & Wahl, M. Tolerance of juvenile barnacles (*Amphibalanus improvisus*) to warming and elevated pCO_2. *Mar. Biol.* **160**, 2023–2035 (2013).
110. Pansch, C., Nasrolahi, A., Appelhans, Y. S. & Wahl, M. Impacts of ocean warming and acidification on the larval development of the barnacle *Amphibalanus improvisus*. *J. Exp. Mar. Biol. Ecol.* **420–421**, 48–55 (2012).
111. Nowicki, J. P., Miller, G. M. & Munday, P. L. Interactive effects of elevated temperature and CO_2 on foraging behavior of juvenile coral reef fish. *J. Exp. Mar. Biol. Ecol.* **412**, 46–51 (2012).
112. Nguyen, H. D., Doo, S. S., Soars, N. A. & Byrne, M. Noncalcifying larvae in a changing ocean: warming, not acidification/hypercapnia, is the dominant stressor on development of the sea star *Meridiastra calcar*. *Glob. Change Biol.* **18**, 2466–2476 (2012).
113. Nguyen, H. D. & Byrne, M. Early benthic juvenile *Parvulastra exigua* (Asteroidea) are tolerant to extreme acidification and warming in its intertidal habitat. *J. Exp. Mar. Biol. Ecol.* **453**, 36–42 (2014).
114. Agnalt, A. L., Grefsrud, E. S., Farestveit, E., Larsen, M. & Keulder, F. Deformities in larvae and juvenile European lobster (*Homarus gammarus*) exposed to lower pH at two different temperatures. *Biogeosciences* **10**, 7883–7895 (2013).
115. Alsterberg, C., Eklöf, J. S., Gamfeldt, L., Havenhand, J. N. & Sundbäck, K. Consumers mediate the effects of experimental ocean acidification and warming on primary producers. *Proc. Natl Acad. Sci. USA* **110**, 8603–8608 (2013).
116. Anlauf, H., D'Croz, L. & O'Dea, A. A corrosive concoction: the combined effects of ocean warming and acidification on the early growth of a stony coral are multiplicative. *J. Exp. Mar. Biol. Ecol.* **397**, 13–20 (2011).
117. Anthony, K. R. N., Kline, D. I., Diaz-Pulido, G., Dove, S. & Hoegh-Guldberg, O. Ocean acidification causes bleaching and productivity loss in coral reef builders. *Proc. Natl Acad. Sci. USA* **105**, 17442–17446 (2008).
118. Appelhans, Y. S. et al. Juvenile sea stars exposed to acidification decrease feeding and growth with no acclimation potential. *Mar. Ecol. Prog. Ser.* **509**, 227–239 (2014).
119. Arnberg, M. et al. Elevated temperature elicits greater effects than decreased pH on the development, feeding and metabolism of northern shrimp (*Pandalus borealis*) larvae. *Mar. Biol.* **160**, 2037–2048 (2013).
120. Baragi, L. V. & Anil, A. C. Interactive effect of elevated pCO_2 and temperature on the larval development of an inter-tidal organism, *Balanus amphitrite* Darwin (Cirripedia: Thoracica). *J. Exp. Mar. Biol. Ecol.* **471**, 48–57 (2015).
121. Baria, M. V. B., Kurihara, H. & Harii, S. Tolerance to elevated temperature and ocean acidification of the larvae of the solitary corals *Fungia fungites* (Linnaues, 1758) and *Lithophyllon repanda* (Dana, 1846). *Zool. Sci.* **32**, 447–454 (2015).
122. Basso, L., Hendriks, I. E. & Duarte, C. M. Juvenile pen shells (*Pinna nobilis*) tolerate acidification but are vulnerable to warming. *Estuaries Coasts* **38**, 1976–1985 (2015).
123. Biscéré, T. et al. Responses of two scleractinian corals to cobalt pollution and ocean acidification. *PLoS ONE* **10**, e0122898 (2015).
124. Brennand, H. S., Soars, N., Dworjanyn, S. A., Davis, A. R. & Byrne, M. Impact of ocean warming and ocean acidification on larval development and calcification in the sea urchin *Tripneustes gratilla*. *PLoS ONE* **5**, e11372 (2010).
125. Brown, M. B., Edwards, M. S. & Kim, K. Y. Effects of climate change on the physiology of giant kelp, *Macrocystis pyrifera*, and grazing by purple urchin, *Strongylocentrotus purpuratus*. *Algae* **29**, 203–215 (2014).
126. Buerger, P., Schmidt, G. M., Wall, M., Held, C. & Richter, C. Temperature tolerance of the coral *Porites lutea* exposed to simulated large amplitude internal waves (LAIW). *J. Exp. Mar. Biol. Ecol.* **471**, 232–239 (2015).
127. Burdett, H. L. et al. Effects of high temperature and CO_2 on intracellular DMSP in the cold-water coral *Lophelia pertusa*. *Mar. Biol.* **161**, 1499–1506 (2014).
128. Burnell, O. W., Russell, B. D., Irving, A. D. & Connell, S. D. Eutrophication offsets increased sea urchin grazing on seagrass caused by ocean warming and acidification. *Mar. Ecol. Prog. Ser.* **485**, 37–46 (2013).
129. Bylenga, C. H., Cummings, V. J. & Ryan, K. G. Fertilisation and larval development in an Antarctic bivalve, *Laternula elliptica*, under reduced pH and elevated temperatures. *Mar. Ecol. Prog. Ser.* **536**, 187–201 (2015).
130. Byrne, M., Soars, N., Selvakumaraswamy, P., Dworjanyn, S. A. & Davis, A. R. Sea urchin fertilization in a warm, acidified and high pCO_2 ocean across a range of sperm densities. *Mar. Environ. Res.* **69**, 234–239 (2010).

131. Byrne, M. et al. Unshelled abalone and corrupted urchins: development of marine calcifiers in a changing ocean. *Proc. R. Soc. B* **278**, 2376–2383 (2011).
132. Byrne, M. et al. Ocean warming will mitigate the effects of acidification on calcifying sea urchin larvae (*Heliocidaris tuberculata*) from the Australian global warming hot spot. *J. Exp. Mar. Biol. Ecol.* **448**, 250–257 (2013).
133. Byrne, M. et al. Effects of ocean warming and acidification on embryos and non-calcifying larvae of the invasive sea star *Patiriella regularis*. *Mar. Ecol. Prog. Ser.* **473**, 235–246 (2013).
134. Byrne, M. et al. Warming influences Mg^{2+} content, while warming and acidification influence calcification and test strength of a sea urchin. *Environ. Sci. Technol.* **48**, 12620–12627 (2014).
135. Byrne, M. et al. Vulnerability of the calcifying larval stage of the Antarctic sea urchin *Sterechinus neumayeri* to near-future ocean acidification and warming. *Glob. Change Biol.* **19**, 2264–2275 (2013).
136. Carey, N. & Sigwart, J. D. Size matters: plasticity in metabolic scaling shows body-size may modulate responses to climate change. *Biol. Lett.* **10**, 20140408 (2014).
137. Castillo, K. D., Ries, J. B., Bruno, J. F. & Westfield, I. T. The reef-building coral *Siderastrea siderea* exhibits parabolic responses to ocean acidification and warming. *Proc. R. Soc. B* **281**, 20141856 (2014).
138. Christensen, A. B., Nguyen, H. D. & Byrne, M. Thermotolerance and the effects of hypercapnia on the metabolic rate of the ophiuroid *Ophionereis schayeri*: inferences for survivorship in a changing ocean. *J. Exp. Mar. Biol. Ecol.* **403**, 31–38 (2011).
139. Cohen-Rengifo, M., Garcia, E., Hernandez, C. A., Hernandez, J. C. & Clemente, S. Global warming and ocean acidification affect fertilization and early development of the sea urchin *Paracentrotus lividus*. *Cah. Biol. Mar.* **54**, 667–675 (2013).
140. Comeau, S., Carpenter, R. C. & Edmunds, P. J. Effects of irradiance on the response of the coral *Acropora pulchra* and the calcifying alga *Hydrolithon reinboldii* to temperature elevation and ocean acidification. *J. Exp. Mar. Biol. Ecol.* **453**, 28–35 (2014).
141. Courtney, T., Westfield, I. & Ries, J. B. CO_2-induced ocean acidification impairs calcification in the tropical urchin *Echinometra viridis*. *J. Exp. Mar. Biol. Ecol.* **440**, 169–175 (2013).
142. Davis, A. R. et al. Complex responses of intertidal molluscan embryos to a warming and acidifying ocean in the presence of UV radiation. *PLoS ONE* **8**, e55939 (2013).
143. Dove, S. G. et al. Future reef decalcification under a business-as-usual CO_2 emission scenario. *Proc. Natl Acad. Sci. USA* **110**, 15342–15347 (2013).
144. Duarte, C. et al. Combined effects of temperature and ocean acidification on the juvenile individuals of the mussel *Mytilus chilensis*. *J. Sea Res.* **85**, 308–314 (2014).
145. Eklöf, J. S. et al. Experimental climate change weakens the insurance effect of biodiversity. *Ecol. Lett.* **15**, 864–872 (2012).
146. Findlay, H. S., Kendall, M. A., Spicer, J. I. & Widdicombe, S. Post-larval development of two intertidal barnacles at elevated CO_2 and temperature. *Mar. Biol.* **157**, 725–735 (2010).
147. Findlay, H. S., Kendall, M. A., Spicer, J. I. & Widdicombe, S. Relative influences of ocean acidification and temperature on intertidal barnacle post-larvae at the northern edge of their geographic distribution. *Estuar. Coast. Shelf Sci.* **86**, 675–682 (2010).
148. Foster, T., Gilmour, J. P., Chua, C. M., Falter, J. L. & McCulloch, M. T. Effect of ocean warming and acidification on the early life stages of subtropical *Acropora spicifera*. *Coral Reefs* **34**, 1217–1226 (2015).
149. García, E., Clemente, S. & Hernández, J. C. Ocean warming ameliorates the negative effects of ocean acidification on *Paracentrotus lividus* larval development and settlement. *Mar. Environ. Res.* **110**, 61–68 (2015).
150. García, E., Clemente, S., López, C., McAlister, J. S. & Hernández, J. C. Ocean warming modulates the effects of limited food availability on *Paracentrotus lividus* larval development. *Mar. Biol.* **162**, 1463–1472 (2015).
151. Gestoso, I., Arenas, F. & Olabarria, C. Ecological interactions modulate responses of two intertidal mussel species to changes in temperature and pH. *J. Exp. Mar. Biol. Ecol.* **474**, 116–125 (2016).
152. Gianguzza, P. et al. Temperature modulates the response of the thermophilous sea urchin *Arbacia lixula* early life stages to CO_2-driven acidification. *Mar. Environ. Res.* **93**, 70–77 (2014).
153. Hardy, N. A. & Byrne, M. Early development of congeneric sea urchins (*Heliocidaris*) with contrasting life history modes in a warming and high CO_2 ocean. *Mar. Environ. Res.* **102**, 78–87 (2014).
154. Hiebenthal, C., Philipp, E. E. R., Eisenhauer, A. & Wahl, M. Effects of seawater pCO_2 and temperature on shell growth, shell stability, condition and cellular stress of Western Baltic Sea *Mytilus edulis* (L.) and *Arctica islandica* (L.). *Mar. Biol.* **160**, 2073–2087 (2013).
155. Ho, M. A., Price, C., King, C. K., Virtue, P. & Byrne, M. Effects of ocean warming and acidification on fertilization in the Antarctic echinoid *Sterechinus neumayeri* across a range of sperm concentrations. *Mar. Environ. Res.* **90**, 136–141 (2013).
156. Iguchi, A., Suzuki, A., Sakai, K. & Nojiri, Y. Comparison of the effects of thermal stress and CO_2-driven acidified seawater on fertilization in coral *Acropora digitifera*. *Zygote* **23**, 631–634 (2015).
157. Inoue, M. et al. Estimate of calcification responses to thermal and freshening stresses based on culture experiments with symbiotic and aposymbiotic primary polyps of a coral, *Acropora digitifera*. *Glob. Planet. Change* **92–93**, 1–7 (2012).
158. Johansen, J. L. & Jones, G. P. Increasing ocean temperature reduces the metabolic performance and swimming ability of coral reef damselfishes. *Glob. Change Biol.* **17**, 2971–2979 (2011).
159. Kamya, P. Z. et al. Larvae of the coral eating crown-of-thorns starfish, *Acanthaster planci* in a warmer-high CO_2 ocean. *Glob. Change Biol.* **20**, 3365–3376 (2014).
160. Kaniewska, P. et al. Major cellular and physiological impacts of ocean acidification on a reef building coral. *PLoS ONE* **7**, e34659 (2012).
161. Kaniewska, P. et al. Transcriptomic changes in coral holobionts provide insights into physiological challenges of future climate and ocean change. *PLoS ONE* **10**, e0139223 (2015).
162. Kavousi, J., Reimer, J. D., Tanaka, Y. & Nakamura, T. Colony-specific investigations reveal highly variable responses among individual corals to ocean acidification and warming. *Mar. Environ. Res.* **109**, 9–20 (2015).
163. Keppel, E. A., Scrosati, R. A. & Courtenay, S. C. Interactive effects of ocean acidification and warming on subtidal mussels and sea stars from Atlantic Canada. *Mar. Biol. Res.* **11**, 337–348 (2015).
164. Kreiss, C. M., Michael, K., Bock, C., Lucassen, M. & Pörtner, H. O. Impact of long-term moderate hypercapnia and elevated temperature on the energy budget of isolated gills of Atlantic cod (*Gadus morhua*). *Comp. Biochem. Physiol. A* **182**, 102–112 (2015).
165. Lannig, G., Eilers, S., Pörtner, H. O., Sokolova, I. M. & Bock, C. Impact of ocean acidification on energy metabolism of oyster, *Crassostrea gigas*—changes in metabolic pathways and thermal response. *Mar. Drugs* **8**, 2318–2339 (2010).
166. Levas, S. et al. Organic carbon fluxes mediated by corals at elevated pCO2 and temperature. *Mar. Ecol. Prog. Ser.* **519**, 153–164 (2015).
167. Li, S. et al. Interactive effects of seawater acidification and elevated temperature on biomineralization and amino acid metabolism in the mussel *Mytilus edulis*. *J. Exp. Biol.* **218**, 3623–3631 (2015).
168. Li, S. et al. Transcriptome and biomineralization responses of the pearl oyster *Pinctada fucata* to elevated CO_2 and temperature. *Sci. Rep.* **6**, 18943 (2016).
169. Lischka, S. & Riebesell, U. Synergistic effects of ocean acidification and warming on overwintering pteropods in the Arctic. *Glob. Change Biol.* **18**, 3517–3528 (2012).
170. Matoo, O. B., Ivanina, A. V., Ullstad, C., Beniash, E. & Sokolova, I. I. Interactive effects of elevated temperature and CO_2 levels on metabolism and oxidative stress in two common marine bivalves (*Crassostrea virginica* and *Mercenaria mercenaria*). *Comp. Biochem. Physiol. A* **164**, 545–553 (2013).
171. Mayor, D. J., Everett, N. R. & Cook, K. B. End of century ocean warming and acidification effects on reproductive success in a temperate marine copepod. *J. Plankton Res.* **34**, 258–262 (2012).
172. Meadows, A. S., Ingels, J., Widdicombe, S., Hale, R. & Rundle, S. D. Effects of elevated CO_2 and temperature on an intertidal meiobenthic community. *J. Exp. Mar. Biol. Ecol.* **469**, 44–56 (2015).
173. Melatunan, S., Calosi, P., Rundle, S. D., Moody, A. J. & Widdicombe, S. Exposure to elevated temperature and PCO_2 reduces respiration rate and energy status in the periwinkle *Littorina littorea*. *Physiol. Biochem. Zool.* **84**, 583–594 (2011).
174. Miller, G. M., Watson, S. A., Donelson, J. M., McCormick, M. I. & Munday, P. L. Parental environment mediates impacts of increased carbon dioxide on a coral reef fish. *Nat. Clim. Change* **2**, 858–861 (2012).
175. Miller, G. Temperature is the evil twin: effects of increased temperature and ocean acidification on reproduction in a reef fish. *Ecol. Appl.* **25**, 603–620 (2015).
176. Engström-Öst, J. & Isaksson, I. Effects of macroalgal exudates and oxygen deficiency on survival and behaviour of fish larvae. *J. Exp. Mar. Biol. Ecol.* **335**, 227–234 (2006).
177. Hagerman, L. & Szaniawska, A. Behaviour, tolerance and anaerobic metabolism under hypoxia in the brackish-water shrimp *Crangon crangon*. *Mar. Ecol. Prog. Ser.* **34**, 125–132 (1986).
178. Winn, R. N. & Knott, D. M. An evaluation of the survival of experimental populations exposed to hypoxia in the Savannah River estuary. *Mar. Ecol. Prog. Ser.* **88**, 161–179 (1992).
179. Baker, S. M. & Mann, R. Effects of hypoxia and anoxia on larval settlement, juvenile growth, and juvenile survival of the oyster *Crassostrea virginica*. *Biol. Bull.* **182**, 265–269 (1992).
180. Hassell, K. L., Coutin, P. C. & Nugegoda, D. Hypoxia impairs embryo development and survival in black bream (*Acanthopagrus butcheri*). *Mar. Pollut. Bull.* **57**, 302–306 (2008).

181. Marcus, N. H., Richmond, C., Sedlacek, C., Miller, G. A. & Oppert, C. Impact of hypoxia on the survival, egg production and population dynamics of *Acartia tonsa* Dana. *J. Exp. Mar. Biol. Ecol.* **301**, 111–128 (2004).
182. Shang, E. H. H. & Wu, R. S. S. Aquatic hypoxia is a teratogen and affects fish embryonic development. *Environ. Sci. Technol.* **38**, 4763–4767 (2004).
183. Mugnier, C., Zippera, E., Goaranta, C. & Lemonnier, H. Combined effect of external ammonia and molt stage on the blue shrimp *Litopenaeus stylirostris* physiological response. *Aquaculture* **274**, 398–407 (2008).
184. Sedlacek, C. & Marcus, N. H. Egg production of the copepod *Acartia tonsa*: the influence of hypoxia and food concentration. *J. Exp. Mar. Biol. Ecol.* **318**, 183–190 (2005).
185. Stalder, L. C. & Marcus, N. H. Zooplankton responses to hypoxia: behavioral patterns and survival of three species of calanoid copepods. *Mar. Biol.* **127**, 599–607 (1997).
186. de Zwaan, A., Cortesi, P., van den Thillart, G., Roos, J. & Storey, K. B. Differential sensitivities to hypoxia by two anoxia-tolerant marine molluscs: a biochemical analysis. *Mar. Biol.* **111**, 343–351 (1991).
187. Cooper, R. U., Clough, L. M., Farwell, M. A. & West, T. L. Hypoxia-induced metabolic and antioxidant enzymatic activities in the estuarine fish *Leiostomus xanthurus*. *J. Exp. Mar. Biol. Ecol.* **279**, 1–20 (2002).
188. Secor, D. H. & Gunderson, T. E. Effects of hypoxia and temperature on survival, growth and respiration of juvenile Atlantic sturgeon, *Acipencer oxyrinchus*. *Fish. Bull.* **96**, 603–613 (1998).
189. Wu, R. S. S., Zhou, B. S., Randall, D. J., Woo, N. Y. S. & Lam, P. K. S. Aquatic hypoxia is an endocrine disruptor and impairs fish reproduction. *Environ. Sci. Technol.* **37**, 1137–1141 (2003).
190. Moher, D. et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* **6**, e1000097 (2009).
191. R Core Team *R: A Language and Environment for Statistical Computing* (R Foundation for Statistical Computing, 2018).
192. Viechtbauer, W. Conducting meta-analyses in R with the metafor. *J. Stat. Softw.* **36**, 1–48 (2010).
193. Viechtbauer, W. *Meta-Analysis Package for R: Package 'metafor'* version 2.4-0 (2019).
194. Knapp, G. & Hartung, J. Improved tests for a random effects meta-regression with a single covariate. *Stat. Med.* **22**, 2693–2710 (2003).
195. Gurevitch, J. & Hedges, L. V. Statistical issues in ecological meta-analyses. *Ecology* **80**, 1142–1149 (1999).

Acknowledgements

This work was supported by the Fundação para a Ciência e Tecnologia (FCT), through the strategic project granted to MARE strategic project (UID/MAR/04292/2019), the PhD grants attributed to E.S. (SFRH/BD/131771/2017), C.S. (SRFH/SFRH/BD/117890/2016) and V.F. (CEECIND/02484/2018), financed by national and community funds from FCT and the European Social Fund (ESF), through the Human Capital Operating Programme and Regional Operation Programme (Lisboa 2020). Furthermore, we acknowledge the DFG Centre of Excellence 2117 'Centre for the Advanced Study of Collective Behaviour' (ID: 422037984), L.A.L. was supported by NSF OCE1829623 and NOAA CHRP award NA18NOS4780172, and H.-O.P. was supported by PACES programme of the AWI and the DFG (German Research Council Po 278 16-1 and -2) Research group Tersane.

Author contributions

E.S., I.C.R. and R.R. conceptualized the study. E.S., I.C.R. and C.S. collected the data. E.S. and V.F. performed the statistical analyses. I.C.R. and C.S. designed the figures. H.-O.P., C.M.D. and L.A.L. supervised work preparation. E.S., I.C.R., C.S., V.F., H.-O.P., C.M.D., L.A.L. and R.R. interpreted data and wrote the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41559-020-01370-3.

Correspondence and requests for materials should be addressed to E.S.

Peer review information *Nature Ecology & Evolution* thanks Christopher Gobler, Jonathan Lefcheck and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

nature research

Corresponding author(s): Eduardo Sampaio

Last updated by author(s): Nov 26, 2020

Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	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)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	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	Data collection was performed using Google Scholar and ISI Web of Knowledge. Data was retrieved from selected peer-reviewed scientific papers, either by direct acquisition of raw data (when available), or using im2graph software (v0.74) to obtain mean, variation and sample size from graphical information within the mentioned selected papers. All data retrieved are present in Supplementary Materials (Supplementary Data 1 and 2).
Data analysis	Data was analyzed using Rstudio version 1.1.463. For the hierarchical mixed-effects meta-analysis, we used the package "metafor" version 1.94. All code used to analyse raw data is available on the file Supplementary Code 1.

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
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Data used for figures and analyses are provided with the submission, in the form of three supporting files: Supplementary Data 1 and 2 (both pertaining to raw data), and Supplementary Code (R code used for analyses).

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences ☐ Behavioural & social sciences ☒ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Ecological, evolutionary & environmental sciences study design

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

Study description	Here we provide a comparative assessment of responses of marine biota to ocean warming (OW), ocean acidification (OA) and hypoxic events (HE), based on hierarchical mixed model meta-analyses of quantitative data collected from the available literature. We calculated interdependent effect sizes for all stressors (OW, OA, OW + OA, and HE), and compared these stressor-specific effects across an array of biological responses (e.g. survival, abundance, energy metabolism, reproduction, and development), and over distinct: i) taxonomic groups (e.g. fish, mollusk, and crustacean); ii) life stages (egg/larva, juvenile and adult); and iii) climate regions (tropical/subtropical and temperate).
Research sample	Using Google Scholar and ISI Web of Knowledge, the available literature was examined for experimental/manipulative studies that gauged the effects of global change-related environmental stressors (i.e. ocean warming – OW; ocean acidification – OA; and hypoxic events – HE) on biological responses of coastal marine biota (e.g. survival, abundance, energy metabolism, reproduction, development). The initial search yielded an initial pool of ~700 studies and ~2000 experiments (Supplementary Data 1).
Sampling strategy	While "warming" and "acidification" were used per se during literature search, a broad definition of future dissolved O2 levels (here defined as moderate hypoxia) was needed to enable the feasibility of a categorical meta-analysis. Given the difficulties in finding adequate trait-based responses in the literature with the keywords "oxygen" or "deoxygenation", the keyword "hypoxia" was used to retrieve studies from which we could measure effects of HE. Searches were carried out with all possible pairwise combinations of stressors, together with the words: "ocean", "sea" or "marine" (e.g. acidification AND warming AND ocean; acidification AND hypoxia AND sea).
Data collection	Data was collected directly from raw data provided with the paper, or alternatively mean, data variation (e.g. standard deviation, standard error) and sample size were collected from text or graphical information within the papers.
Timing and spatial scale	Studies published between 1st January 1990 (roughly marking the emergence of experimental studies directly assessing the effects of global change in marine biota; see Supplementary Figure 1) and 1st March 2016 (end of search) were considered.
Data exclusions	Exclusions were driven by pre-formed criteria (see Methods). Also not considered were studies where quantitative stressor values were missing, controls were not suitable, pH was changed using acid addition, and any form of data variation (i.e. standard deviation, standard error, confidence intervals or variance) was not reported or was not possible to determine. Given our hierarchical approach, for a detailed description of the number of studies removed at each step of the process, please see the flow diagram elaborated following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Figure 2).
Reproducibility	All data and code required to repeat the analyses are available together with manuscript submission. There were no failed attempts of reproducing this study and the results obtained.
Randomization	Randomization was not relevant to this study, since we collected already available experimental data.
Blinding	Blinding was not relevant to this study.

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