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A meta-analysis of gas bubble trauma in fish

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Abstract

Total dissolved gas (TDG) supersaturation generated by dams is known to cause gas bubble trauma (GBT) and mortality in fish, but despite many studies on the topic, there have been no recent attempts to systematically review the data. We conducted a systematic review and meta-analysis to determine how different levels of TDG supersaturation in laboratory experiments impact mortality and GBT outcomes of freshwater fishes. We also examined all TDG laboratory studies on freshwater fish to identify research gaps in the GBT literature. Factors that improved the linear mixed-effects models and Cox proportional hazards models of the relationship between TDG supersaturation and time to 50% mortality, time to 10% mortality, time to the appearance of bubbles in the gills and time to external GBT symptoms include depth, temperature, oxygen-to-nitrogen ratios, species, body mass, the interaction between TDG and depth and author group for one or more of the models of the relationship between TDG and GBT outcomes. Of the 99 GBT studies we found in our search, 74% quantified mortality outcomes, with limited assessment of quantitative behavioural, histological and performance outcomes. Moreover, the majority of studies were conducted on salmonids. We therefore recommend additional studies on non-salmonid species to enhance our understanding of the mechanisms of GBT and community effects with use of more diverse sublethal outcomes. We also recommend random subject allocation to treatments, complete reporting, consistent methods between treatments and the use of control groups (which were often lacking) for more rigorous experimental designs.

KEYWORDS

conservation, dams, gas bubble disease, supersaturation, systematic review, total dissolved gas, total gas pressure

1 | INTRODUCTION

There is currently a worldwide proliferation of dams, with 59 000 hydroelectric dams over 15 m high registered with the International Commission On Large Dams (2018). Furthermore, there are an additional 3,700 hydroelectric dams over 1 megawatt (MW) planned or under construction as of 2015 (Zarfl, Lumsdon, Berlekamp, Tydecks, & Tockner, 2015). Once these dams are constructed, the number of large, free-flowing rivers worldwide will be further reduced by 21% (Zarfl et al., 2015). These numbers do not account for the proliferation of small hydroelectric dams; Couto and Olden (2018) estimate that there exist over 82,000 small hydropower dams worldwide (≤10 MW or based on each country's definition of small hydropower dams). Currently, only 37% of rivers longer than 1,000 kilometres are free-flowing over their entire length (Grill et al., 2019). Most new dams are being built in countries with developing and emerging economies (Zarfl et al., 2015), where important benefits include electricity generation, control of water supply, low flow

augmentation, flood control and improved navigation. Many of the sites where new dams are being built are also regions of high biodiversity (Winemiller et al., 2016) with important subsistence fisheries (Mcintyre, Reidy, & Revenga, 2016). This is of concern because dams threaten biodiversity as a result of waterway connectivity loss, altered habitats and changes in flow regimes and sediment transport. One of the important but lesser known effects of dams on aquatic life is gas bubble trauma (GBT) as a result of total dissolved gas (TDG) supersaturation.

Total dissolved gas supersaturation has long been known to cause GBT in aquatic animals, and the external symptoms have been described in detail. The first thorough descriptions were made at Woods Hole Oceanographic Institute (e.g. Gorham, 1898, 1901), where mortality and observed GBT in fish were determined to be the result of accidental TDG supersaturation. Research on GBT accelerated in the late 1960s when it was discovered that spill from dams was generating TDG supersaturation in the Columbia River system and was harming threatened salmonids (e.g. Ebel, 1971; Meekin & Allen, 1974). Early studies described the pathology of GBT, which includes a diversity of direct effects on fish such as gas bubbles in the lateral line, under the skin, in the mouth, in and on the gills, in the blood, behind the eyes and in other tissues. Swim bladder over-inflation has also been reported (Krise & Herman, 1989; Shrimpton, Randall, & Fidler, 1990a,1990b). These symptoms can cause indirect effects such as haemorrhaging, tissue necrosis (Stroud, Bouck, & Nebeker, 1975), infection (Schisler, Bergersen, & Walker, 2000; Stroud et al., 1975), impaired development (Cornacchia & Colt, 1984; Counihan, Miller, Mesa, & Parsley, 1998; Geist, Linley, Cullinan, & Deng, 2013), positive buoyancy (Shrimpton et al., 1990a,1990b), changes in behaviour (Dawley, Monk, Schiewe, Ossiander, & Ebel, 1976; Lund & Heggberget, 1985; Shrimpton, Randall, & Fidler, 1990a) and mortality.

Whereas many of the symptoms of GBT in fish have been identified, determining the relationships between TDG supersaturation and effects on fish is complicated by the many factors that modify the severity of GBT. Intrinsic factors that affect the severity of GBT can include body size (Krise & Herman, 1991; Rucker, 1975; Shrimpton et al., 1990a), life stage (Bouck, Nebeker, & Stevens, 1976; Counihan et al., 1998; Geist et al., 2013), species (Bouck et al., 1976; Dawley, Monk, et al., 1976; Mesa, Weiland, & Maule, 2000), and possibly stock (Gray, Page, & Bronzi, 1982) and behaviour. Extrinsic factors such as depth (Antcliffe, Fidler, & Birtwell, 2002; Fickeisen & Montgomery, 1978; Pleizier, Nelson, Cooke, & Brauner, 2020), temperature (Ebel, Dawley, & Monk, 1971; Fickeisen, Montgomery, & Hanf, 1974; Nebeker, Hauck, & Baker, 1979) and oxygen-to-nitrogen ratios (Jensen, 1988; Nebeker, Bouck, & Stevens, 1976; Nebeker et al., 1979) have also been demonstrated to affect GBT. Given the many factors influencing the severity of GBT, it is not surprising that defining guidelines for safe levels of TDG for fish has been challenging.

Regulations for TDG levels near dams are based on narrative reviews of the GBT literature as well as specific studies. For example, the limit for TDG supersaturation in Washington State is 110% TDG, based on evidence from the US National Marine Fisheries Service (2000) and monitoring data cited as a personal communication from Schneider (*in* Pickett & Harding, 2002), and a literature review in which the references are not disclosed (Pickett & Harding, 2002). The state permits short-term exemptions to this limit in the Snake and Columbia Rivers (Oregon Department of Environmental Quality & Washington State Department of Ecology, 2009), based on a review of 28 bioassay studies, 15 fish depth distribution studies (Maynard, 2008), two reviews (Schneider, 2008; Weitkamp, 2008) and biological monitoring data from 1995 to 2007. The British Columbia guidelines for TDG is approximately 110% TDG (the guideline is 76 mmHg gauge pressure, which is equivalent to 110% TDG at a barometric pressure of 760 mmHg) (Fidler & Miller, 1994) based on a meta-analysis of 32 papers on the time to mortality of salmonids at various levels of TDG supersaturation (Fidler, 1988). Both the Washington and BC regulations are based on a wealth of experimental data and conclusions made in reviews. These reviews offer valuable insight, but most use approaches to collecting and reporting the existing data that are not systematic (but see Fidler, 1988; Jensen, Schnute, & Alderdice, 1986) and their assessments of the quality of the available data are not transparent (but see Fidler, 1988). The meta-analysis conducted by Fidler (1988) indicates that the 110% TDG guideline is conservative for Pacific salmonids in most cases, but there are some studies in which TDG supersaturation has caused

symptoms of GBT (Dawley, Schiewe, & Monk, 1976; Espmark, Hjelde, & Baeverfjord, 2010; Shrimpton, Randall, & Fidler, 1990b) and mortality (*Ameiurus melas*, Gray, Page, Saroglia, & Festa, 1983) at levels below 110%. TDG guidelines are best supported by analyses that are as objective as possible of data that is comprehensive and up to date.

During the writing of a traditional review, the author makes subjective choices which introduce bias; this bias can be minimized using the process of systematic review. This process incorporates strict protocols for searching the literature, screening for relevant documents and extracting data. This generates a comprehensive literature search which can produce repeatable results (Haddaway, Woodcock, Macura, & Collins, 2015; The Cochrane Collaboration, 2011). If the data are quantitative, meta-analysis can be used to further describe the data and define relationships. Because the rigorous methods of full systematic reviews can be prohibitively resource intensive, several groups have developed methods for reducing bias and improving the transparency of reviews without using a full systematic review protocol (Collins, Miller, Coughlin, & Kirk, 2014; Haddaway et al., 2015; UK Civil Service, 2010). In this review, we use aspects of systematic review methods to create a robust meta-analysis of the relationship between TDG supersaturation and GBT in freshwater fish in laboratory experiments and to identify future research opportunities. To address these objectives, we structured the review around two primary questions: (1) How do different levels of TDG supersaturation in laboratory experiments impact mortality and GBT outcomes of fishes in freshwater? (2) What are the research gaps in the study of the effects of TDG supersaturation on fishes in freshwater laboratory studies?

We model the time to 10% mortality, 50% mortality, bubbles in the gills and external GBT using linear mixed-effects models and Cox proportional hazards models. To our knowledge, studies by Fidler (1988) and Jensen et al. (1986) are the only meta-analyses of time to mortality data in TDG supersaturation. Additional data have been generated on the topic over the past two decades, and new statistical approaches can be used to update previous analyses.

Based on previous research, there are extrinsic factors that we predict will improve our models of GBT. We predict that increased depth will decrease the hazard of mortality, gas bubbles in the gills and external GBT based on evidence that depth protects fish from GBT (Antcliffe et al., 2002; Fickeisen & Montgomery, 1978; Pleizier et al., 2020). Several studies have demonstrated that temperature effects the hazard of mortality as a result of GBT, but the direction of the relationship differs by species and acclimation time (Bouck et al., 1976; Nebeker et al., 1979); thus, we predict that temperature will improve all models but we do not predict the direction of the relationship. We also predict that increases in the molar oxygen-to-nitrogen ratio will reduce the hazard of mortality based on results from Rucker (1975) and Nebeker et al. (1976), Nebeker et al. (1979) and will reduce the hazard of gas bubbles in the gills.

There are also several intrinsic factors that we predict will improve our models. Several studies indicate that larger (Rucker, 1975) and older fish (e.g. Geist et al., 2013; Krise & Herman, 1991; Nebeker, Andros, McCrady, & Stevens, 1978) have an increased hazard of mortality from GBT; for this reason, we predict that the hazard of mortality and GBT in the gills will increase with fish size. Given that external symptoms of GBT are in tissues that are in close contact with the environment, we predict that external symptoms of GBT may be more strongly affected by the external environment than the internal environment of the fish and thus predict that fish size will not improve the model of external GBT. Based on multiple studies in which species differences in GBT were observed (Bouck et al., 1976; Dawley, Schiewe, et al., 1976; Mesa et al., 2000), we predict that species will improve the models of the hazard mortality, bubbles in the gills and external GBT. Given the focus on mitigating GBT mortality effects on salmonids in the Columbia River system, we predict that there is a paucity of data on the lethal and sublethal effects of TDG supersaturation on non-salmonid species.

2 | METHODS

2.1 | Systematic data collection

The protocol for this review was based on methods recommended by the UK Civil Service (2010), the Cochrane Collaboration (2011), Collins et al. (2014) and Haddaway et al. (2015). Search strategies were developed based on the two questions stated in the introduction. The questions were divided into their subject population, experimental intervention, comparator and outcomes/end points and search strings were created based on these components (Table S1). As questions 1 and 2 had the same subject populations, interventions and comparators, the same search string was used for both questions (Table S1). Thirteen databases were searched (Table S1), with database coverage including scientific journal articles, graduate theses, government reports, conference proceedings and other grey literature. Unfortunately, Google Scholar searches are not consistent over time or between users; despite this, Google Scholar was used because it yielded many relevant documents that were not found in other databases. Search strings were adapted to the format of database search engines when necessary (Table S1).

The search was completed 3 March 2016 and yielded 4,880 unique documents, of which 47 met the criteria for question 1 and 99 met the criteria for question 2. We removed the databases Science.gov and ProQuest Dissertations & Theses Global from the search because they returned over 1 million and 2,600 documents, respectively, of which very few met our criteria. Google Scholar restricts the number of document citations that can be downloaded; for this reason, of the 1,760 documents returned by string #1 we could only download 400, and of the 213 documents returned by string #2, we could only download 160. Google Scholar sorts citations by relevance, so that the citations downloaded were the most relevant based on Google Scholar criteria. Of the 4,259 documents returned by ScienceDirect, 2,685 were book chapters. Because these book chapters did not appear to contain primary research, we restricted the search to journal articles for this database. For the same reason, we restricted the search in SpringerLink to "Article type" documents. When organized by library and relevance, we were not able to access

articles numbered 1,021–1,030 from the Worldcat database. Several criteria were added during the screening process, but all the criteria were used to screen all the studies.

Each study returned by the search was screened using the same criteria. For all studies, the author, year and title were collected, and duplicates were removed. Based on the criteria in Table S2, documents were removed if their titles indicated that they were not primary reports of laboratory experiments on the effects of TDG supersaturation on fish in freshwater. Studies were not removed if their relevance was uncertain. During the second round of screening, the studies were screened based on their abstracts, using the same criteria as the first round of screening. During the third round of screening, studies were screened based on their methods, using the original screening criteria, as well as additional criteria (Table S2), which categorized the studies based upon which of the current review's research questions they addressed. The references cited in the studies that fulfilled the screening criteria were added to the search and screened using the same process. The references in these additional studies, as well as the references of the studies collected using inter-library loans, were not added to the literature search.

Data were extracted during the third round of screening. Briefly, to address question 1 information describing the study animals, the experimental conditions, the experimental variables and the experimental outcomes/end points were extracted from each study (see the Appendix for the complete dataset). For question 2, information on the study animals, the treatment conditions and the experimental conditions for all available data for time to 10% mortality, time to 50% mortality, time to the appearance of GBT on the exterior of the fish (including bubbles under the skin, between the fin rays, under the epithelium of the buccal cavity and exophthalmia, but excluding bubbles in the lateral line) and time to the first appearance of bubbles in the blood vessels of the gills were collected. These data were collected for each experimental replicate if possible; otherwise, the mean or cumulative values of all replicates in each treatment group were collected. Studies were not included if none of the treatments reached one of our end points (10% or 50% mortality, bubbles in the gills or external GBT).

In addition to the data extraction described above, all studies were assessed for their risk of bias. The Cochrane Collaboration (2011) recommends criteria for assessing the risk of bias in studies on healthcare interventions. Unfortunately, the rigour used in healthcare research is rarely used in aquatic research. For this reason, a less rigorous version of the Cochrane Collaboration criteria was developed for the current study (Table S3). The categories of bias assessed included selection bias, performance bias and detection bias. Selection bias can occur when subjects are not randomly allocated to treatment groups. Selection bias was assessed by determining whether subjects were randomly allocated to treatment groups. Performance bias occurs when different treatment groups are exposed to different degrees of care or other conditions unrelated to experimental interventions of interest. This type of bias is usually reduced by blinding researchers to the treatments each group is receiving. Unfortunately, blinding is rarely done in fisheries studies. As an alternative, it was recorded whether studies used control groups and/or before-and-after observations for comparisons with treatment groups. Blinding is also used to prevent detection bias, which occurs when there are differences in the assessment of experimental outcomes in different treatment groups. As an alternative criterion, it was determined whether outcomes were assessed in the same way for each treatment group. Each study was rated for their risk of bias in each of these categories; risk of bias was assessed as high, low, or unknown. The risk of bias was also assessed for each data point collected for question 1. During analysis, high risk and unknown risk of bias were grouped together. One of the authors (NP) executed all the screening and data extraction.

To identify any inconsistencies in the screening and data extraction process, another author (DA) repeated the screening protocol for 20 randomly selected titles and repeated the data extraction protocol for seven studies. DA compared results with those of NP. Multiple discrepancies were discovered in screening and data extraction, although most discrepancies were inconsequential. When responses differed between the authors, the differences were discussed and resolved. For data categories in which DA identified errors, inconsistencies, or for which it was decided to resolve methodical differences in favour of DA's assessment, NP revised the dataset accordingly.

2.2 | Statistical analysis

Time to 50% mortality data, time to 10% mortality data, time to gas bubbles in the gills and time to gas bubbles on the exterior of the fish were each modelled using two methods. All analyses were conducted in the R environment (R Core Team, 2019). We conduct linear regressions of the uncensored data for these parameters, where uncensored data refer to treatment groups that have reached the experimental end point of interest before the experiment is terminated. Right-censored data refer to treatment groups that have not reached the experimental end point of interest before the experiment is terminated. Censored data are less informative than uncensored data but nevertheless provide time to event data up to the point at which the treatment is terminated. We incorporate censored data into the analysis of the datasets of time to 50% mortality, time to 10% mortality, time to gas bubbles in the gills and time to gas bubbles on the exterior of the fish using Cox proportional hazards models. This model is a regression of the exponential relationship between the time to an event (e.g. time to 50% mortality) and predictor variables, with the inclusion of an unknown baseline hazard. This function is used to estimate hazard ratios for each covariate. For categorical data, hazard ratios describe the hazard rate of each group compared to a reference group. For continuous covariates, the hazard ratio describes the change of the hazard per unit of that variable; hazard ratios less than one indicate a decrease in hazard with an increase in the covariate, hazard ratios greater than one indicate an increase in hazard with an increase in the covariate. Treatment groups included in the model datasets had access to different ranges of depth; exploratory modelling indicated that maximum depth available to the fish improved the models of outcome variables relative to median or minimum depth available to the fish.

For this reason, maximum depth is used as a fixed effect in models instead of median or minimum depth.

2.3 | Breakpoint analysis

It was observed that the relationship between per cent TDG and the log-transformed time to 50% mortality was not linear; there appears to be a breakpoint in the relationship at high TDG levels. It was reasoned that the processes that lead to bubble growth and mortality in TDG supersaturated conditions may require a certain amount of time to proceed; that is, bubble growth and mortality at very high TDG are not instantaneous. For this reason, a breakpoint analysis was conducted to determine where the relationship changes. The R function "segmented" (package "segmented"; version 1.1-0; Muggeo, 2019) was used to fit a regression model of time to 50% mortality with a segmented relationship between time to 50% mortality and per cent TDG with one breakpoint. Maximum depth available, temperature, the molar oxygen-to-nitrogen ratio and species were also included as fixed effects in the model. A breakpoint at 137% TDG improved the model (AIC 348) relative to the linear model (AIC 362). Based on this breakpoint, we removed all data with TDG treatments ≥ 137% TDG ($n = 67$) from the dataset for the linear model of log-transformed time to 50% mortality, in order to build a more accurate regression at lower TDG values.

The procedure was repeated to identify a breakpoint in the time to 10% mortality data, with the same fixed effects included in the model. A segmented relationship between time to 10% mortality and the per cent TDG with one breakpoint improved the model, but the breakpoint was at 117% TDG, which was not relevant in describing changes in time to mortality at high TDG levels. When the procedure was repeated with two breakpoints, there was one breakpoint at 118% TDG and another at 138% TDG. For the reasons described for the time to 50% mortality data, all four observations with TDG treatments greater or equal to 138% were removed from the dataset used to create the linear model of time to 10% mortality.

Breakpoint analysis was not possible for the data for time to appearance of bubbles in the gills given the distribution of the data; observations with TDG greater than 137% were removed from the dataset for the linear model of the log-transformed time to appearance of bubbles in the gills. The dataset for the time to the appearance of external GBT did not have a breakpoint at high TDG levels because there are no TDG values greater than 131%. Observations with high TDG treatments were not removed for any of the Cox models.

2.4 | Linear models of censored data

2.4.1 | Linear mixed-effects models for time to 10 and 50 per cent mortality

Linear mixed-effect models of natural logarithm of time to 10% and 50% mortality were built using the "lmer" function from the R environment (package "lme4"; Bates, Maechler, Bolker, & Walker, 2019). As described above, data for TDG ≥ 137% were not included in the models of time to 50% mortality or time to bubbles in the gills and data for TDG ≥ 138% were not included in the model of time to 10% mortality based on the results of the breakpoint analysis and the appearance of the relationship between TDG and time to mortality. For the model of time to 50% mortality, the results of Levene's test of the optimal model indicated heterogeneity of variance for the factor TDG ($F = 7.08$, $p = .009$), largely as a result of an outlying observation at 3,725 hr of exposure to 112% TDG. Greater variance in longer exposures might be expected as a result of adventitious factors such as TDG fluctuations and infection. The final model is presented with this observation removed, which reduced heterogeneity of variance for TDG ($F = 4.14$, $p = .04$). In the model of the time to 10% mortality, there was heterogeneity of variance for the ratio of oxygen to nitrogen ($F = 4.58$, $p = .03$). The natural logarithm transformation of the oxygen-to-nitrogen ratio resulted in homogeneity of variance ($F = 3.25$, $p = .07$); we present the optimal model with this transformation. Mean times to 10% and 50% mortality were weighted by the number of replicates averaged for each datapoint, because the information needed to estimate variation within treatments was not available in many studies. If the number of replicates was not reported, it was assumed that there was no replication. Data reported as cumulative mortality were treated as unreplicated. The full model included mean per cent TDG saturation, maximum depth available, temperature, the molar oxygen-to-nitrogen ratio, mean body mass and species as fixed effects. Stage of development was not included as a fixed effect because it caused perfect separation of the outcome data. Data were assigned to groups based on whether they shared common authors and these author groups were included as random intercepts in the model. If an author group had only one observation in a model dataset, the author group was combined with the next smallest author group. The drop1 function was used to compare the AIC value of the full model to reduced models with one factor removed, with a threshold of 2 AIC units to determine whether two models were different. Once the model was selected, it was compared in the same way to an additional model with an added interaction between mean per cent TDG saturation and maximum depth to determine whether the interaction improved the model. Confidence intervals were calculated using the confint.merMod function (package "lme4"; Bates et al., 2019) using bootstrapping with 1,000 simulations.

2.4.2 | Linear models for time to bubbles in the gills

The natural logarithm of time to the appearance of bubbles in the gills was modelled using the same methods as time to 10% and 50% mortality. Random effects for author groups did not improve the model, so the data were modelled using the linear model function ("lm" function, R Core Team, 2019). In the gill bubble data, periodic sampling to monitor for these symptoms was often unreplicated; for this reason, the data for the time to appearance of bubble in the

gills were weighted by the number of fish sampled in each sampling period rather than using the number of replicates. Furthermore, the ratio of molar oxygen to nitrogen was not included as a fixed effect in our models because five out of six studies did not report dissolved oxygen levels during the experiment.

2.4.3 | Linear mixed-effects models for time to external GBT

The full linear model of the natural logarithm of time to the appearance of external GBT was modelled with mean per cent TDG saturation, maximum depth available, temperature, fish body mass and species as fixed effects. The full model with body mass as a fixed effect only includes data from one author group, so author group was not included as a random effect and the data were modelled using the linear model function. The ratio of molar oxygen to nitrogen was not included as a fixed effect because none of the studies in the dataset for the full model reported oxygen levels. Because the inclusion of body mass as a fixed effect reduces the sample size from $n = 30$ to $n = 23$, an additional model was built without body mass as a fixed effect. The model without body mass includes multiple author groups, but the inclusion of author group overfit the model, so the model was constructed without random effects. Variance across species groups was heterogeneous; for this reason, weights by species variance (varIdent()) were added to the optimal model once it had been chosen, and the model was created using generalized least squares ("gls" function; R Core Team, 2019).

Cox proportional hazards models

2.4.4 | Cox mixed-effects model for time to 10 and 50 per cent mortality

The hazard of both 10% and 50% mortality was each modelled using the "coxme" package from the R environment (version 2.2-14; Therneau, 2019a). The Cox proportional hazards model is expressed by the hazard function (Equation 1), in which $h(t)$ is the hazard function, which is the probability of having an event occur at time t given that the subject has survived until that time; h_0 is the baseline hazard, which is the hazard if all the coefficients (b_i) are equal to zero; x_i are the covariates, which are the factors that effect the time to an event; and b_i are the coefficients of the covariates, which indicate the effect size of the covariates. This function is used to estimate hazard ratios for each covariate. In the models, mean time to 10% and 50% mortality was weighted by the number of replicates. Data that were reported as cumulative mortality were treated as unreplicated. The full model included mean per cent TDG saturation, maximum depth available, temperature, the molar oxygen-to-nitrogen ratio, body mass and species as fixed effects. As in the linear models, groups based on common authors were included as random intercepts in the model. Penalized AIC values were used to compare the full model to reduced models, with a threshold of 2 AIC units. Once all the variables were selected and necessary transformations were made, the linear model was compared in the same way to one with the interaction between mean per cent TDG saturation and maximum depth to determine whether the interaction improved the model. The optimal Cox mixed-effects model was run using the coxph function (package "survival," version 3.1-8; Therneau, 2019b), with random intercepts specified as offsets, to estimate coefficient standard errors and confidence intervals and to use diagnostic tools to examine the model for influential cases, proportional hazards and linearity. Linear models were compared with models with penalized splines with two degrees of freedom for each fixed effect in turn to check for linearity. If a fixed effect was non-linear, the penalized spline was included in a model; interactions were not included in spline models because a spline model could not be compared with a model containing an interaction.

$$h(t) = h_0(t) \times \exp(b_1 x_1 + b_2 x_2 + \ldots b_p x_p) \quad (1)$$

2.4.5 | Cox mixed-effects model for time to bubbles in the gills and external gas bubble trauma

The hazard of bubbles in the gills and bubbles on the exterior of the fish was both modelled using the same methods as the models for 10% and 50% mortality. In the gill data, periodic sampling to monitor for these symptoms was often not replicated; for this reason, the data for the time to appearance of bubble in the gills were weighted by the number of fish sampled in each sampling period instead of the number of replicates.

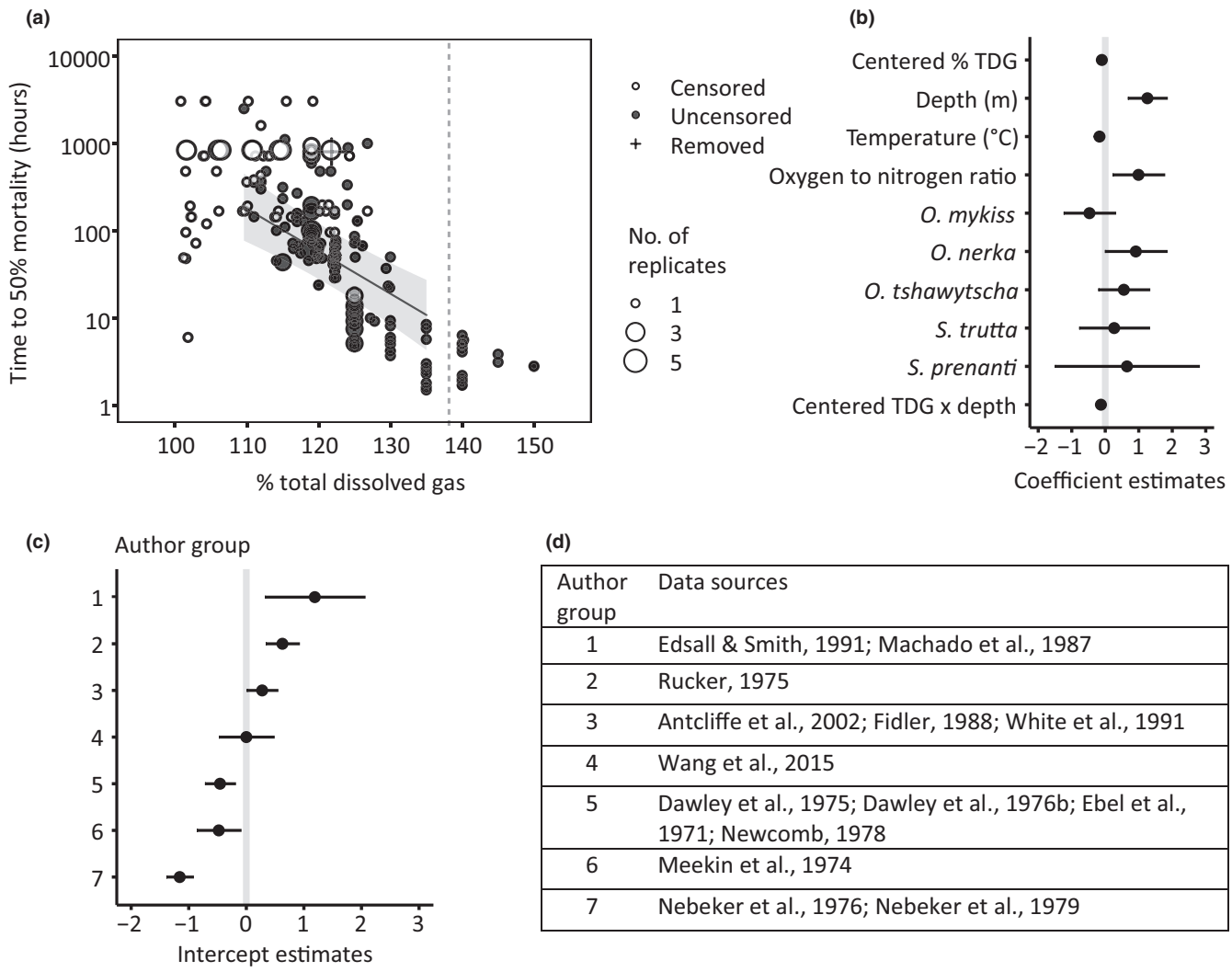
3 | RESULTS

3.1 | Linear models of censored data

3.1.1 | Model of 50% mortality

The dataset for the optimal model (Equation 2) of the natural logarithm of the uncensored time to 50% mortality data with TDG values ≤ 137% included 120 observations from 14 different studies. Species represented are coho salmon (*Oncorhynchus kisutch*, Salmonidae), rainbow trout and steelhead trout (*Oncorhynchus mykiss*, Salmonidae), sockeye salmon (*Oncorhynchus nerka*, Salmonidae), chinook salmon (*Oncorhynchus tshawytscha*, Salmonidae), brown trout (*Salmo trutta*, Salmonidae) and ya-fish (*Schizothorax prenanti*, Cyprinidae). The dataset included one observation for Lake trout (*Salvelinus namaycush*, Salmonidae). This observation was removed to prevent perfect separation. The inclusion of fish body mass as a fixed effect did not improve the model (Table S4) and reduced the sample size from $n = 120$ to $n = 92$, so body mass was removed from the analysis and subsequent models were built with the inclusion of data that were previously omitted. The model fits a linear relationship between log-transformed time to 50% mortality and the fixed

effects (Equation 2). The optimal model includes mean per cent TDG saturation, maximum depth available in metres, temperature in °C, the molar oxygen-to-nitrogen ratio, species and the interaction between mean per cent TDG saturation and depth as fixed effects and author group as random intercepts (Table S4, model 9). The marginal *R*-squared value of the optimal model is 0.50, and the conditional *R*-squared value is 0.81. The optimal model can be described using the following equation (Equation 2), where LT50 is the estimated time to 50% mortality in hours, %TDG is the per cent TDG at the water surface, h is the depth in metres, T is temperature in degrees Celsius, O_2:N_2 is the molar ratio of oxygen to nitrogen, and species is the intercept for each species (Table S5; Figure 1). The inclusion of the interaction between TDG and depth makes the main effect for depth difficult to interpret because the range of per cent TDG does not include zero, so we present the model equation with per cent TDG centred on the mean (%TDG - 123), to facilitate the interpretation of the depth coefficient. The residuals for TDG are somewhat skewed compared to a normal distribution. Greater values of standardized β in Table S5 indicate a stronger correlation between a continuous fixed effect and log time to 50% mortality. Based on the standardized β values for the optimal model, mean TDG had the greatest effect, followed by depth and temperature, and then the interaction between TDG and depth. The continuous factor with the smallest effects was the oxygen-to-nitrogen ratio. The time to 50% mortality decreases as TDG and temperature increase, whereas increased depth and oxygen-to-nitrogen ratios prolong the time to 50% mortality. In examining the intercepts for each species, we observe that *O. mykiss* reaches 50% mortality most rapidly, followed by coho



(d)

Author group	Data sources
1	Edsall & Smith, 1991; Machado et al., 1987
2	Rucker, 1975
3	Antcliffe et al., 2002; Fidler, 1988; White et al., 1991
4	Wang et al., 2015
5	Dawley et al., 1975; Dawley et al., 1976b; Ebel et al., 1971; Newcomb, 1978
6	Meekin et al., 1974
7	Nebeker et al., 1976; Nebeker et al., 1979

FIGURE 1 Meta-analysis of time to 50% mortality of fish in freshwater exposed to total dissolved gas (TDG) supersaturation in laboratory experiments. (a) The relationship between TDG and time to 50% mortality. Data include 162 observations and 109 events from 13 studies comprising seven species. All data were used to build a Cox proportional hazards models (Table S11) and uncensored data from treatments < 137% TDG (dashed line) were included in the linear mixed-effects model (Table S5, eq. 2). The black line represents the relationship between TDG and time to 50% mortality at 0.08 m depth from the linear mixed-effects model, with the 95% CI in grey. (b) Coefficient estimates for the linear mixed-effects model of time to 50% mortality with 95% CI. The molar oxygen-to-nitrogen ratio was used in the model. (c) Random effects in the linear model of time to 50% mortality for groups sharing common authors. (d) The data sources included in each author group

salmon, brown trout, chinook salmon, ya-fish and sockeye salmon. It should be noted, however, that the 95% confidence interval for each species is large (Table S5; Figure 1).

$$LT50 = \exp^{(5.23-0.10(\%TDG-123)+1.26(h)-0.17(T)+0.99(O2:N2)+species-0.13((\%TDG-123)\times h)} \quad (2)$$

3.1.2 | Model of 10% mortality

The optimal model (Equation 3) of the uncensored, log-transformed time to 10% mortality data with TDG ≤ 138% included 105 observations from ten studies. Species include coho salmon, *O. mykiss*, chinook salmon, brown trout and lake trout. The fixed effect for fish body mass did not improve the model (Table S6) and reduced the sample size from $n = 105$ to $n = 65$, so it was removed, and subsequent models included data that were previously omitted. The optimal model fits a relationship between the natural logarithm of the time to 10% mortality and the fixed effects (Equation 3). The optimal model includes mean per cent TDG saturation, maximum depth available, the oxygen-to-nitrogen ratio and species as fixed effects, with random intercepts for author group (Figure 2, Tables S6) and S7). The marginal R-squared value of the optimal model is 0.51 and the conditional *R*-squared value is 0.77. Taking into consideration the confidence interval of the model (Table S7), the time to 10% mortality can be modelled using Equation 3, where LT10 is the estimated time to 10% mortality in hours, with all other symbols as in Equation 2. The species intercept values are found in Table S7. The residuals for the fixed effects are somewhat skewed but approximate the normal distribution. Based on the standardized β values for the factors in the optimal model, mean TDG had the strongest relationship with time to 10% mortality, followed by the oxygen-to-nitrogen ratio, and depth (Table S7). Time to 10% mortality decreases as TDG increases, whereas increased depth and oxygen-to-nitrogen ratios were associated with an increase in the time to 10% mortality. The intercepts for species indicate that *O. mykiss* reaches 10% mortality most rapidly, followed by coho salmon, brown trout, chinook salmon and lake trout. The coefficient standard errors for some species are large relative to the coefficient estimate (Table S7).

$$LT10 = \exp^{(25.25-0.17(\%TDG)+0.83(h)+1.58(\ln(O2:N2))+species)} \quad (3)$$

3.1.3 | Model of time to bubbles in the gills

The dataset for the time to the appearance of bubbles in the gills includes 150 observations from seven studies (Figure 3). The species longnose sucker (*Catostomus catostomus*, Catostomidae), largescale sucker (*Catostomus macrocheilus*, Catostomidae), *O. mykiss*, chinook salmon, northern pikeminnow (*Ptychocheilus oregonensis*, Cyprinidae), redside shiner (*Richardsonius balteatus*, Cyprinidae) and walleye (*Sander vitreus*, Percidae) are represented in the dataset. The fixed effect for body mass improved the model but reduced the sample size from 150 to 25, so the factor was removed from the model and data previously omitted were added back into the dataset. The optimal model of the log-transformed time to the appearance of bubbles in the gills includes the fixed effects mean TDG, depth, temperature and species. There was significant heterogeneity of variance for the fixed effects for temperature and species. Replacing the weights by sample size with weights based on a variance structure within each species (varIdent(); R Core Team, 2019) caused heterogeneity in the fixed effect for TDG. For this reason, we do not present a model for time to bubbles in the gills.

3.1.4 | Model of the time to external GBT

The generalized least-squares model (Equation 4) of the natural logarithm of time to the appearance of external GBT was built with a dataset of 30 observations from six studies, with data weighted by variance within species. The data include values for the species white sturgeon (*Acipenser transmontanus*, Acipenseridae), longnose sucker, largescale sucker, *O. mykiss*, chinook salmon, northern pikeminnow, redside shiner and walleye. The inclusion of fish body mass as a fixed effect did not improve the model (Table S8) and reduces the sample size from $n = 30$ to $n = 23$, so it was removed from the model and subsequent models included data that were previously omitted. The model includes mean TDG and species as factors (Figure 4, Table S8, Equation 4). The *R*-squared value of the model is 0.86. Taking into consideration the confidence interval of the model (Table S9), the time to external GBT can be modelled using the following equation (Equation 4), where eGBT is the estimated time to the appearance of external GBT symptoms in hours, with all other symbols as in Equation 2. White sturgeon exhibits external signs of GBT most rapidly, followed by *O. mykiss*, chinook salmon, largescale sucker, northern pikeminnow, redside shiner, longnose sucker and walleye.

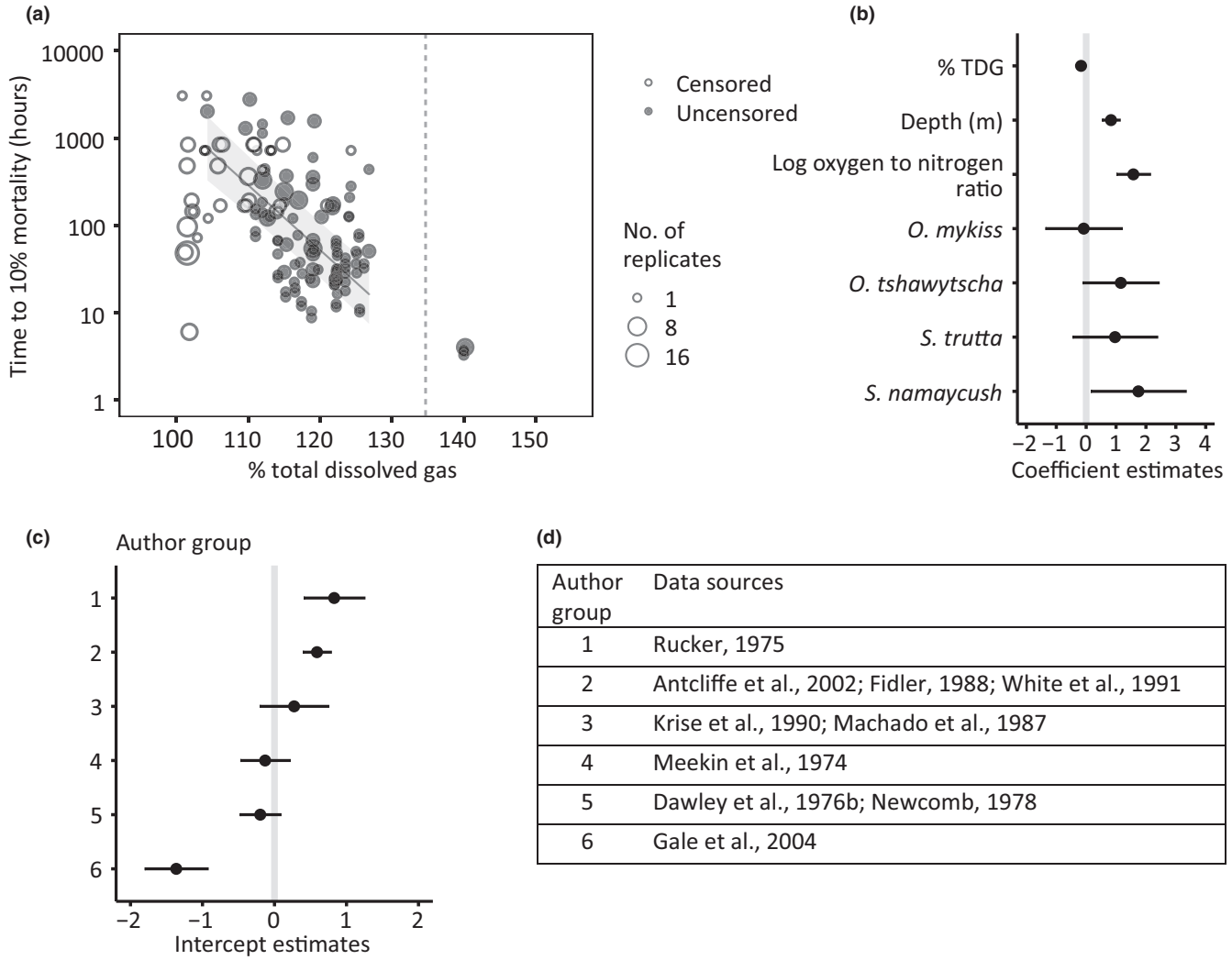
$$eGBT = \exp^{(12.86-0.11(\%TDG)+species)} \quad (4)$$

Cox proportional hazards models

3.1.5 | Model of the hazard of 50% mortality

Model including body mass as a fixed effect

The data for the models of the hazard of 50% mortality which include body mass as a fixed effect (Table S10, models 1–3; Table S11 "Spline model", "Linear model") contained 162 observations and 109 events from 13 different studies. Species represented in the data include coho salmon, *O. mykiss*, sockeye salmon, chinook salmon, brown trout, lake trout and ya-fish. The optimal model included all the factors, mean per cent TDG saturation, the maximum depth available to the fish, the water temperature, the ratio of molar oxygen-to-molar nitrogen, fish body mass, the species and author group as a random effect (concordance = 0.94; Table S10, model 3; Table S11 "Spline model"). In comparing the AIC of the linear model with the AIC of models with penalized splines for each fixed effect, we determined that TDG was non-linear (Table S10, model 1 compared to



(d)

Author group	Data sources
1	Rucker, 1975
2	Antcliffe et al., 2002; Fidler, 1988; White et al., 1991
3	Krise et al., 1990; Machado et al., 1987
4	Meekin et al., 1974
5	Dawley et al., 1976b; Newcomb, 1978
6	Gale et al., 2004

FIGURE 2 Meta-analysis of time to 10% mortality of fish in freshwater exposed to total dissolved gas (TDG) supersaturation in laboratory experiments. (a) The relationship between TDG and time to 10% mortality. The data include 146 observations and 109 events from 11 studies with 5 species represented. All data were used to build a Cox proportional hazards model (Table S13); uncensored data from TDG treatments < 137% (dashed line) were included in the linear mixed-effects model (Table S7, Equation 3). The black line represents the relationship between TDG and time to 10% mortality from the linear mixed-effects model, with the 95% CI in grey. (b) Coefficient estimates for the linear mixed-effects model of time to 10% mortality with 95% CI. The molar oxygen-to-nitrogen ratio was used in the model. (c) Random effects in the linear mixed-effects model of time to 10% mortality for groups sharing common authors. (d) The data sources included in each author group

model 3), so in the optimal model includes penalized splines for TDG (Table S10, model 3; Table S11 "Spline model"). Given the sample size, the pspline function overfits the data even when using the lowest degree of freedom possible ($df = 2$), yielding extremely large hazard ratios (Table S11, "Spline model") and reducing the predictive power of the model. When examining the relationship between the fixed effects and the Martingale residuals, as well as the plot of regression terms for the spline model against the fixed effect, a linear regression (Table S11 "Linear model") appeared to be a suitable approximation of the relationship between TDG and the hazard of 50% mortality.

Model without body mass as a fixed effect

Including body mass as a fixed effect reduced the number of observations in the hazard models of time to 50% mortality from 208 to 162 and the number of events from 141 to 109; for this reason, we also tested models without body mass as a factor and included the data that were previously omitted (Table S10, models 4–13; Table S11 "Spline model without body mass", "Linear model without body mass"). The dataset for the models without body mass includes data from 18 studies and the species coho salmon, *O. mykiss*, sockeye salmon, chinook salmon, brown trout, lake trout and ya-fish. In comparing the linear models with penalized splines for each fixed effect, we determined that both TDG and depth were non-linear (Table S10, models 10 and 11). The pspline function overfits the data in this case, resulting in large hazard ratios (Table S11 "Spline model without body mass"). When examining the relationship between the fixed effects and the Martingale residuals as well as the plot of regression terms for the spline model against

the fixed effects, a linear regression appeared to be a suitable approximation of the relationship between TDG and the hazard of 50% mortality. With the addition of an interaction between TDG and depth (Table S10, model 13; Table S11 "Linear model without body mass"), a linear regression would also be a suitable approximation of the relationship between depth and the hazard of 50% mortality. The optimal spline model without body mass is included in the Table S11 ("Spline model without body mass"), but in our results and discussion, we present only the linear model (Table S10, model 13; Table S11 "Linear model without body mass"). The linear model for the hazard of 50% mortality without body mass as a factor (concordance = 0.92; Table S10, model 13; Table S11 "Linear model without body mass") includes the mean per cent TDG saturation, the maximum depth available to the fish, the water temperature, the ratio of molar oxygen-to-molar nitrogen, the species, the interaction between mean per cent TDG saturation and depth, and the author group as a random effect. Note that per cent TDG is centred on the mean (% TDG-121) for this model so that the fixed effect for depth is interpretable.

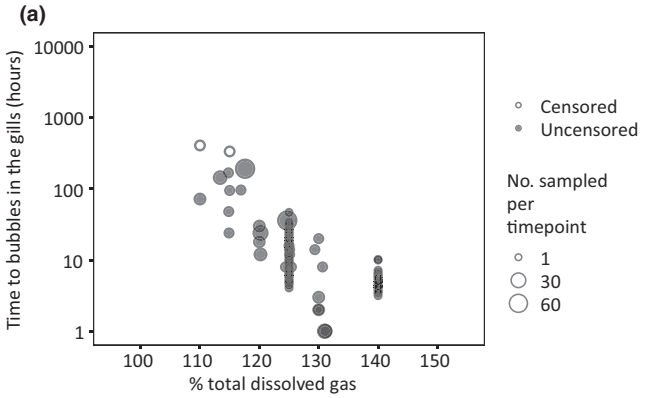


FIGURE 3 Meta-analysis of time to the appearance of bubbles in the gills of fish in freshwater exposed to total dissolved gas (TDG) supersaturation in laboratory experiments. (a) The relationship between TDG and time to bubbles in the gills. The data include 272 observations and 270 events from 7 studies with 7 species. (b) The references for the data sources

Based on the linear model without body mass as a factor, the hazard ratio for TDG (1.21) indicates that, for a fish at the surface, for each 1% increase in per cent TDG, there was a 21%, 95% CI [14, 28], increase in the instantaneous hazard of 50% mortality, given that the fish had survived up to that time. Conversely, increased depth protected fish from mortality, such that at 121% TDG (mean TDG of the dataset), for each metre increase of depth, there was a 96%, 95% CI [88, 99], reduction in the instantaneous hazard of 50% mortality. Temperature increased the hazard of 50% mortality, with a 29%, 95% CI [15, 44], increase in the hazard for each increase of 1°C. With each increase of the molar ratio of oxygen to nitrogen of one, there is a 96%, 95% CI [88, 98], reduction in the hazard of 50% mortality. Based on the model, *O. mykiss* had the greatest instantaneous hazard of 50% mortality, followed by chinook salmon, coho salmon, brown trout, ya-fish and lake trout, and sockeye salmon had the lowest hazard. However, based on the confidence intervals of the hazards ratios, only the hazard ratios of *O. mykiss* (1.24, 95% CI [0.66, 2.31]) and coho salmon (reference group, hazard = 1) were significantly higher than lake trout (0.13, 95% CI [0.03, 0.54]), ya-fish (0.16, 95% CI [0.05, 0.50]) and sockeye salmon (0.06, 95% CI [0.03, 0.15]).

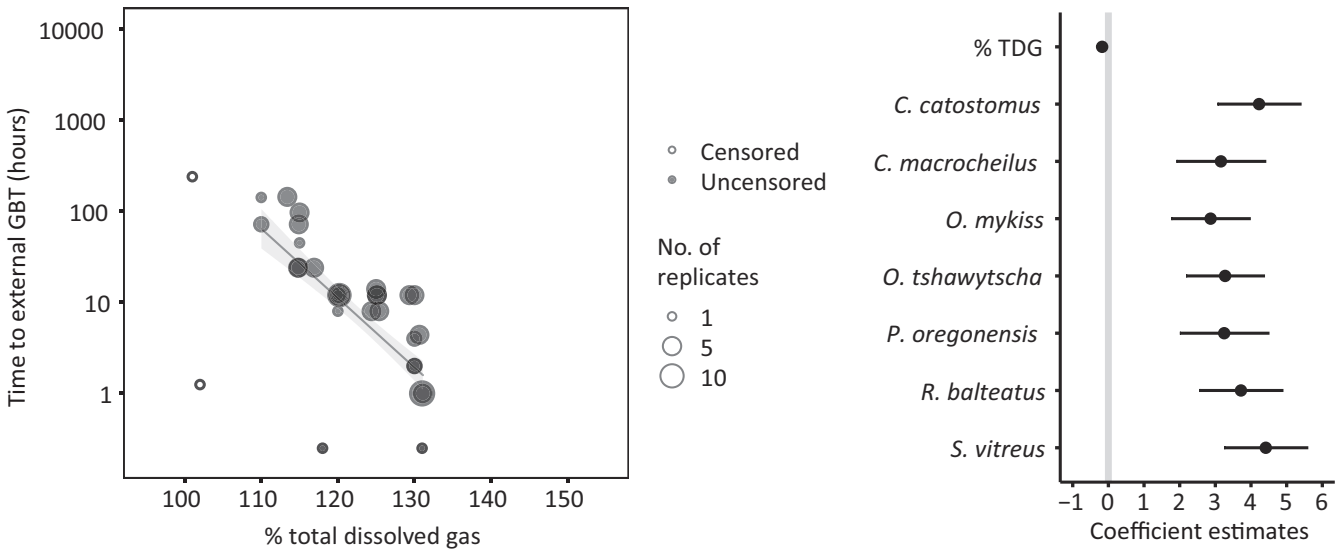


FIGURE 4 Meta-analysis of time to the appearance of external gas bubble trauma (GBT) symptoms in fish in freshwater exposed to total dissolved gas (TDG) supersaturation in laboratory experiments. (a) The relationship between TDG and time to external GBT. The data include 34 observations and 30 events from 6 studies with 8 species represented. Uncensored data were included in the linear model (Table S9, Equation 4). The black line represents the relationship between TDG and time to external GBT, with the 95% CI in grey. (b) Coefficient estimates for the linear model of time to external GBT with 95% CI

3.1.6 | Model of the hazard of 10% mortality

The data for the models of the hazard of 10% mortality (Tables S12; S13) without body mass as a fixed effect include 146 observations and 109 events from 11 different studies. Species represented in the data include coho salmon, *O. mykiss*, chinook salmon, brown trout and lake trout. Fish body mass was not included as a fixed effect because it reduced the number of observations from 146 to 93 and did not significantly improve the fit of the model; we built all the subsequent models with the inclusion of data that were previously omitted in the model with body mass as a fixed effect (Table S12, models 3–12). The larger dataset allowed for the inclusion of species as a fixed effect. The linear model (concordance = 0.90; Table S12, model 9; Table S13 "Linear model") and spline model (concordance = 0.90; Table S12, model 10; Table S13 "Spline model") that were the best fits for the hazard of 10% mortality include mean per cent TDG saturation, maximum depth available to fish and species as fixed effects. Author group was included as a random effect. When the AIC of the linear model was compared to the AIC of a model with a penalized spline for TDG (Table S12, model 9 compared to model 10), there was evidence that the model was improved by the spline fit. However, based on both the relationship between TDG and the Martingale residuals and the plot of the regression terms for the spline model against the fixed effect, a linear regression appeared to be a suitable approximation of the relationship between TDG and the hazard of 10% mortality. Thus, for the reasons described in the results for the model of the hazard of 50% mortality, we report only the results of the linear model (Table S12, model 9; Table S13 "Linear model") in detail.

Based on the linear model, with each 1% increase in TDG, there was a 31%, 95% CI [27, 36], increase in the hazard of 10% mortality (Table S13). With each metre increase in depth, there was a 78%, 95% CI [67, 85], reduction in the hazard of 10% mortality. Coho salmon had the greatest instantaneous hazard of 10% mortality, followed by *O. mykiss*, chinook salmon, brown trout and lake trout. Based on the confidence intervals of the hazards ratios, the hazards ratio of coho salmon (reference group, hazard = 1) was significantly greater than all other species, and the hazard for *O. mykiss* (0.45, 95% CI [0.25, 0.80]) was significantly greater than lake trout (0.05, 95% CI [0.02, 0.13]).

3.1.7 | Model of the hazard of gas bubbles in the gills

The data for the hazard of bubbles in the gills included 272 observations and 270 events from 7 different studies. Species represented in the data include longnose sucker, largescale sucker, *O. mykiss*, chinook salmon, northern pikeminnow, redside shiner and walleye. No starting model estimate was successful with species as a fixed effect, so this factor was not included in the full model. Oxygen partial pressure was reported in only 3 of the 7 studies, so the molar ratio of oxygen to nitrogen was not included as a fixed effect in the models. The model violates the assumptions of proportional hazards and linearity, so it was decided not to pursue further modelling and we do not report the models of the data. The violations of proportional hazards and linearity are likely the result of a dataset dominated by data from two treatment groups reported by Fidler (1998). The relationship between TDG and time to bubbles in the gills is plotted in Figure 3.

3.1.8 | Model of the hazard of external gas bubble trauma

The data for the hazard of external gas bubble trauma included 34 observations and 30 events from 6 different studies (Figure 4). Species represented in the dataset are white sturgeon, longnose sucker, largescale sucker, *O. mykiss*, chinook salmon, northern pikeminnow, redside shiner and walleye. Because water oxygen content was not reported in any of the studies, it was not included as a fixed effect in the models. Including author group as a random effect did not improve the model, so it was not included. The original full model would not converge when species was included as a factor, so species was omitted. Fish body mass was removed as a factor because it reduced the number of observations from 34 to 23 and did not significantly improve the fit of the model (Table S14, model 1 compared to model 2); all the subsequent models were built with the inclusion of data that were previously omitted in the model with body mass as a fixed effect (Table S14, models 3–9), which allowed species to be included as a fixed effect in subsequent models. The best fit linear model (concordance = 0.99, Table S14, model 9; Table S15 "Linear model") included mean per cent TDG saturation and species as fixed effects. When the best fit linear model was compared to a penalized spline model, the relationship between TDG and the hazard of external GBT was discovered to be significantly non-linear (Table S14, model 9 compared to model 10). Again, based on the relationship between the TDG and the Martingale residuals and the plot of regression terms for the spline model against the fixed effect, a linear regressing appeared to be an adequate approximation of the relationship; thus, given the reasons described in the results for the model of the hazard of 50% mortality, we include the penalized spline model in supplementary information (Table S15 "Spline model") but only discuss the results of the linear model (Table S15 "Linear model") in detail.

Based on the linear model (Table S14, model 9; Table S15 "Linear model"), with each 1% increase in TDG, there was a 59%, 95% CI [45, 74], increase in the hazard of external GBT. White sturgeon had the greatest instantaneous hazard of external GBT, followed by *O. mykiss*, largescale sucker and northern pikeminnow, chinook salmon, redside shiner, longnose sucker and walleye. Based on the confidence intervals of the hazards ratios, the hazards ratio of white sturgeon (reference group, hazard = 1) was significantly greater than all

other species, and the hazard for *O. mykiss* (0.04, 95% CI [8.06×10^{-3}, 0.17]) was significantly greater than walleye (7.99×10^{-4}, 95% CI [1.10×10^{-4}, 5.83×10^{-3}]).

3.2 | Research gaps and scope of previous research

For our second research question, we examined the research gaps in the study of the effects of TDG supersaturation on fishes in freshwater laboratory studies. The data revealed that many different types of outcomes, intrinsic factors and extrinsic factors have been assessed with respect to the effects of TDG on fish in laboratory studies. The most frequently assessed outcome was mortality (Figure 5), which was reported in 74% of the 99 studies examined. The next most frequently reported outcomes were bubble growth on the exterior of the fish (58% of studies) and behavioural observations (26%). Whereas a variety of sublethal effects have been examined, much of the data is qualitative (e.g. behaviour and histological data). Of the factors potentially affecting the severity and progression of GBT, comparisons between species have been most frequently studied (30% of studies; Figure 6). The next most frequently studied factors are depth/pressure (19%) and ontogeny/age (17%) effects. Of the 35 species in our dataset, salmonids were the most frequently studied; 83% of all studies included at least one salmonid species (Figure 7). The three most studied species were *O. mykiss* in 47% of the studies, chinook salmon in 34% of the studies and coho salmon in 17% of the studies. All the papers included in this review, including information on the study subjects, experimental conditions, outcomes measured and potential sources of bias can be found in the supplementary material (Appendix).

3.3 | Potential sources of bias in the literature

Of the potential sources of bias (i.e. selection, performance and detection bias (Table S2)), all were frequently observed (Figure 8). Seventy-eight per cent of studies contained at least one experiment where subjects either were not randomly assigned to treatment groups, or the authors did not report that they had randomly assigned subjects to treatment groups. The next most frequently observed source of bias was selective reporting; 38% of studies had at least one treatment group (including controls) for which the stated outcome of interest was not reported. Thirty-six per cent of studies contained at least one experiment in which outcomes were not assessed using the same procedure for all treatment groups. In addition, 25% of studies contained at least one experiment which did not use either a control treatment or a before-and-after design.

4 | DISCUSSION

4.1 | Response to research questions

Our review process enabled us to address both of our initial research questions. For our first question, we conducted a meta-analysis to determine how different levels of TDG supersaturation in laboratory experiments impact mortality and GBT outcomes of fishes in freshwater. We found that exponential models best describe the relationship between the GBT outcomes and per cent TDG levels, as well as other independent variables. As predicted, our models indicate that increased depth is related to longer times to mortality in TDG supersaturated exposures, but the inclusion of depth

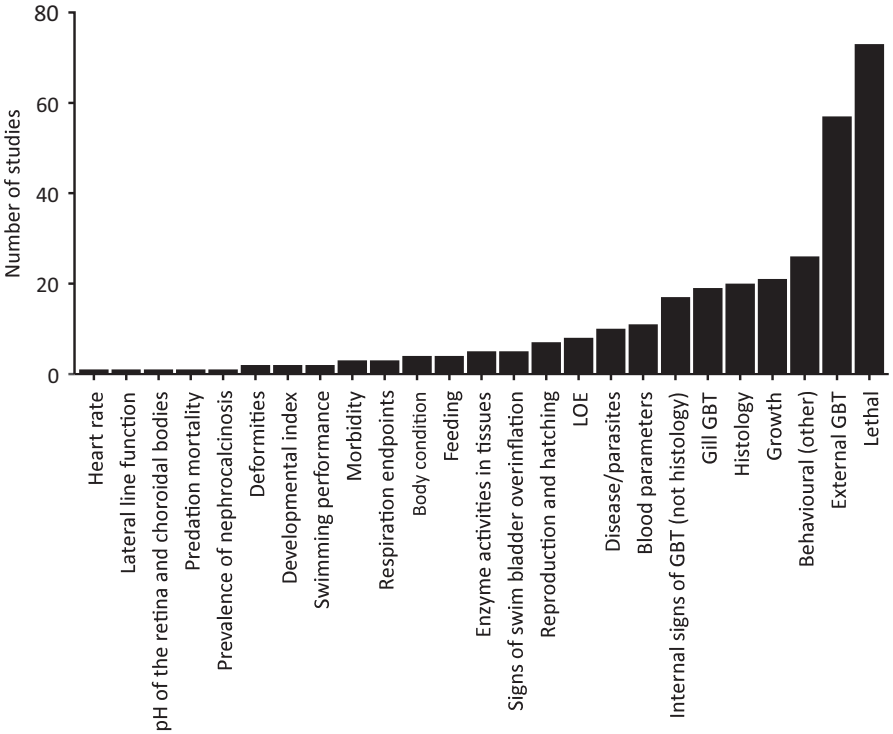


FIGURE 5 The number of studies reporting each outcome type in all laboratory studies used in this meta-analysis on the effects of TDG supersaturation on freshwater fish ($n = 99$)

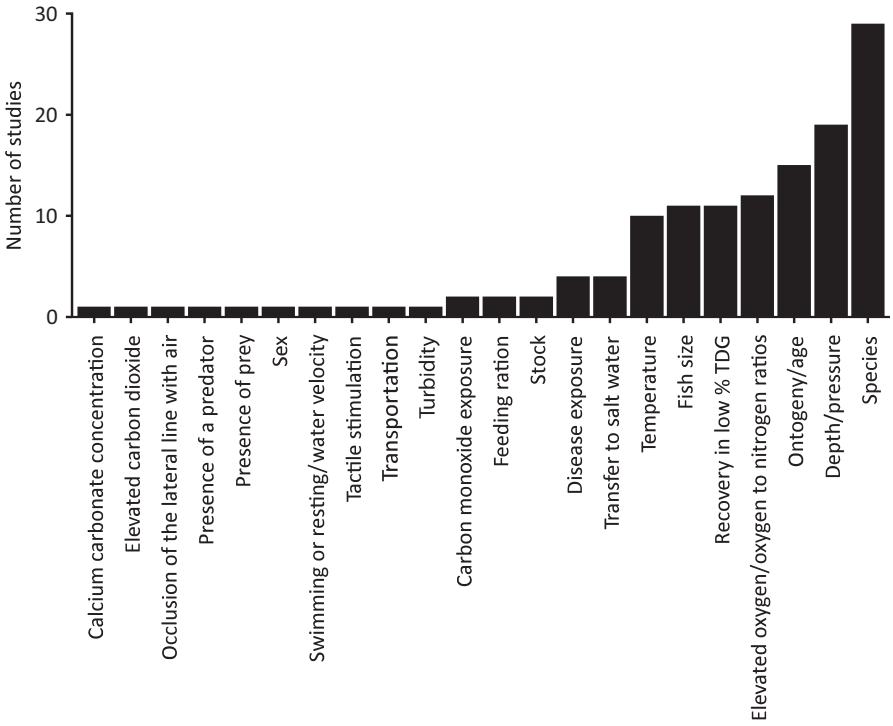


FIGURE 6 The number of studies testing the effect of each type of factor in all laboratory studies used in this meta-analysis on the effects of TDG supersaturation on freshwater fish ($n = 99$)

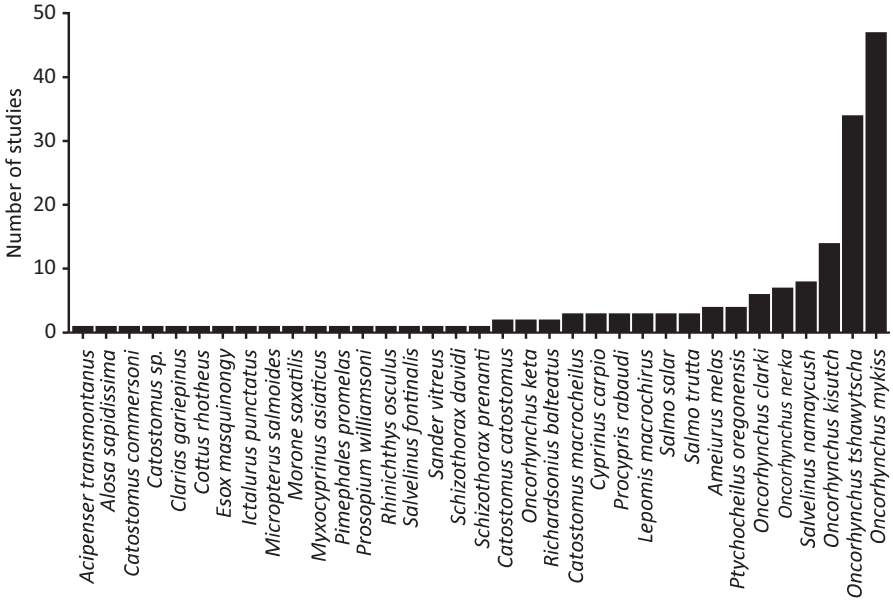


FIGURE 7 The number of laboratory studies on the effects of TDG supersaturation on freshwater fish used in this meta-analysis that includes each fish species ($n = 99$)

did not improve the model of time to external GBT. As predicted, temperature improved the model of time to 50% mortality and time to bubble in the gills; increased temperature is related to decreases in time to 50% mortality. Temperature did not improve any of the other models. As predicted, increasing oxygen-to-nitrogen ratios were related to increased time to mortality in both the linear models of uncensored mortality data but oxygen-to-nitrogen ratios did not improve the models of external GBT. Contrary to predictions, oxygen-to-nitrogen ratios did not improve the Cox model of the hazard of 10% mortality. Body mass did not improve the models of uncensored mortality data but did improve the Cox model of the hazard of 50% mortality, such that larger fish had a greater hazard of mortality. Body mass did not improve the models of external GBT. As anticipated, species improved models of time to mortality and external GBT. Our second question was what are the research gaps in the study of the effects of TDG supersaturation on fishes in freshwater laboratory studies? We found that whereas a diverse suite of factors and outcomes have been assessed, key gaps remain in the literature, such as the effects of activity and behaviour on GBT outcomes. As predicted, salmonids dominate the existing research, and there is much opportunity to study the effects of TDG on other important species.

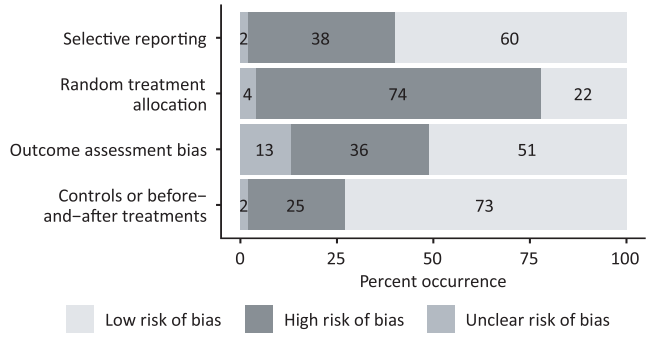


FIGURE 8 Per cent occurrence of risk of bias in laboratory studies used in this meta-analysis on the effects of total dissolved gas supersaturation on freshwater fish ($n = 99$)

4.2 | Time to 50% mortality

Both the model of the uncensored time to 50% mortality data and the model of the hazard of 50% mortality were improved by including TDG, depth, temperature, the molar oxygen-to-nitrogen ratio and species as fixed effects in the model. Body mass improved the Cox model of time to 50% mortality but was not included in all models because it reduced the sample size by 22% (from $n = 208$ to $n = 162$).

Depth protects fish from the effects of TDG (Pleizier et al., 2020). This occurs because hydrostatic pressure reduces the growth of bubbles and can cause them to collapse when the external pressure exceeds the pressure inside a bubble, as described by the Laplace equation for bubble stability,

$$P_i = P_{\text{amb}} + 2 \cdot \frac{\sigma}{r} \quad (5)$$

in which P_i is the internal pressure of the bubble, P_{amb} is the external pressure (the sum of atmospheric pressure, hydrostatic pressure and system pressure), σ is the surface tension of the interface between the gas and the liquid, and r is the bubble radius. The pressure outside a bubble increases as depth increases, as described by the equation for hydrostatic pressure,

$$P = \rho \cdot g \cdot h \quad (6)$$

in which P is the hydrostatic pressure, ρ is the density of water, and g is gravitational acceleration (9.81 m/s^2), and h is the depth. This increased pressure with depth reduces bubble growth in fish tissues. Multiple studies have demonstrated the effect of depth on time to mortality in fish (Antcliffe et al., 2002; Ryan & Dawley, 1998; Shrank, Dawley, & Ryan, 1995), and Pleizier et al. (2020) quantitatively demonstrate the relationship between depth and GBT in TDG supersaturated water in juvenile rainbow trout.

The mechanism by which increased temperature decreases the time to mortality in TDG supersaturated water is unknown. It is interesting that we found a negative relationship between temperature and time to 50% mortality, given that we would expect temperature to increase survival up to the species' optimal temperature and then to decrease beyond that. In past studies that investigated the effect of temperature on mortality in TDG supersaturation, results are mixed depending on the species and the duration of acclimation (e.g. Bouck et al., 1976; Nebeker et al., 1979). Because our dataset is dominated by salmonids, which are generally cold-water species, it may be that increases in experimental temperature were generally challenging for the fish. Although multiple experiments have run different TDG treatments at different temperatures (Figure 6), few have tested the effects of temperature acclimation on survival in TDG supersaturation, which would be an important avenue for future research.

The relationship between the oxygen-to-nitrogen ratio and mortality is intuitive. Oxygen fuels aerobic metabolism in fish tissues, whereas gaseous nitrogen is not consumed. When the water is supersaturated with TDG but the molar oxygen-to-nitrogen ratio approaches one, oxygen consumption in the tissues reduces the TDG pressure inside the fish and reduces the risk of GBT. Oxygen that has not been consumed for metabolism nevertheless contributes to the total gas pressure in fish tissues, and GBT will result at very high tensions (e.g. Edsall & Smith, 1991). For this reason, one would expect the time to mortality to be very long at high oxygen-to-nitrogen ratios, unless TDG is very high.

The mechanisms that underpin the relationship between fish body mass and mortality are unknown. Rucker (1975) found that smaller coho salmon fingerlings survived longer in TDG supersaturation than larger fish of the same age. Similarly, Krise and Herman (1991) found that smaller, younger juvenile Atlantic salmon (*Salmo salar*, Salmonidae) and lake trout had longer times to mortality than larger, older juveniles. To understand how size effects the hazard of mortality, we must know the mechanisms by which TDG causes mortality, which are not fully understood. Some of the effects of body size on mortality are likely related to ontogeny. For example, there is evidence that alevins are less vulnerable to mortality from GBT than salmonids at later stages (Geist et al., 2013; Krise & Herman, 1989; Nebeker et al., 1978). Unfortunately, ontogeny is confounded with body mass in our models. It is important to consider that some species differ in their depth use with ontogeny and season. For this reason, managers should consider whether certain life stages of some species are at greater risk of GBT based on their depth use.

Despite the many species comparisons in the literature (Figure 6), the mechanisms that underlie species differences in GBT have not been determined. If blockage of the blood vessels of the gills by bubbles is causing suffocation in TDG supersaturation, one would expect differences in hypoxia tolerance and gill morphology to drive species differences in time to mortality. In the case of long exposures to low levels of TDG, differences in vulnerability to disease might drive differences in time to mortality between species. An experimental approach that compares GBT between species based on key physiological differences could help elucidate the mechanisms of mortality as a result of GBT.

4.3 | Time to 10% mortality

The model of the uncensored time to 10% mortality data was improved by including TDG, depth, oxygen-to-nitrogen ratios and species as factors, whereas the model of hazard of 10% mortality was improved by including only TDG, depth and species as factors, but not the ratio of molar oxygen to nitrogen. As the same factors are likely to affect both the 10% and 50% mortality, it is possible that temperature, the ratio of molar oxygen to nitrogen and body mass did not improve one or both of the models of 10% mortality because the sample size for time to 10% mortality ($n = 146$ observations for the Cox mixed-effects model without body mass as a fixed effect) is smaller than for time to 50% mortality ($n = 208$ observations for the Cox mixed-effects model without body mass as a fixed effect).

4.4 | Time to bubbles in the gills

We observed an exponential relationship between the uncensored data for the time to the appearance of bubbles in the gills and TDG but we were not able to model the relationship. Based on the time to bubbles in the gills (Figure 3) compared to time to 10% mortality (Figure 2), it appears as though bubbles do not necessarily form in the gills prior to mortality. This is misleading, however, because there is evidence that fish that die of GBT generally have bubbles in the gills (e.g. Antcliffe et al., 2002; Bentley, Dawley, & Newcomb, 1976; Pleizier et al., 2020). It should also be noted that sampling intervals varied greatly in both the time to bubbles in the gills dataset (mean 15.8h ± 6 SE) and the mortality dataset (e.g. 15.0h ± 4 SE for LT10). Furthermore, bubbles tend to form first in the afferent arterioles of the gills, which are difficult to observe because they are partly obscured by the efferent arterioles in whole gills. Given that suffocation as a result of bubbles in the gills is one of the putative causes of mortality from GBT, additional studies of the relationship between TDG and time to bubbles in the gills would be of interest.

4.5 | Time to external gas bubble trauma

The models of the time to external GBT were improved by including per cent TDG and species as factors but not by including depth, temperature and body mass. Because bubbles under the skin and between the fin rays are in close contact with the environment, we might expect them to be influenced more by the external environment than by intrinsic factors. Surprisingly, the inclusion of depth did not improve either of the models of time to external GBT. It is difficult to conclude whether factors did not improve the model based on their effects on bubble growth or because the sample sizes for the linear model ($n = 30$) and the Cox model ($n = 34$) are small. White sturgeon was the most vulnerable species to external GBT in both models, but it should be noted that data were only available for fish of this species that were 1–6 days of age. Caution should be used when estimating species differences in external GBT models because sample sizes for some species are small; five of the eight species in both models were represented by only 2 or 3 datapoints. Exterior GBT is known to be strongly correlated with mortality in *O. mykiss* and chinook salmon at high levels of TDG (130% TDG; Mesa et al., 2000), but we suspect that it is not the cause of mortality, except in extreme cases. Nevertheless, severe cases of external GBT may have important sublethal effects on fish including eye damage as a result of exophthalmia and reduced immunity as a result of damage to fins, skin and the mucous layer of the fish.

4.6 | Model implications

To our knowledge, this is the first attempt to build mixed-effects models and hazard models of mortality and external GBT. We note, however, that Jensen et al. (1986) performed a meta-analysis of the time to 50% mortality of salmonids using a tabular histogram and modelled using a dose–response curve and that Fidler (1988) also performed a meta-analysis of the time to mortality data for salmonids but without incorporating statistical models. Using a Cox proportional hazards model has the advantage of incorporating censored data, as well as building a statistical model that incorporates multiple factors. In addition, given that the last meta-analysis was conducted in 1988 (i.e. Fidler, 1988), much additional data has become available for analysis.

The models we present can be used to estimate the hazard of 50% and 10% mortality, and the time to external GBT and their confidence intervals under different scenarios for multiple species. The models also support previous findings that depth, temperature, oxygen-to-nitrogen ratios, fish size and species all affect the hazard of mortality of fish in TDG supersaturated water. Depth appears to be a particularly important factor in the time to mortality in TDG supersaturated water. Conveniently, the relationship between depth and hydrostatic pressure is easily described (Equation 6) and experimental evidence indicates that the protective effect of depth on GBT in fish is approximately 9.7% TDG per metre depth in freshwater (Pleizier et al., 2020). Using this information, depth could be incorporated in guidelines for allowable TDG supersaturation. The models also reveal that species is an important factor in vulnerability to mortality and external GBT. *O. mykiss* and coho salmon appear to be particularly vulnerable, which suggests that these species might be sensitive models for the effects for the effects of TDG on fish. The number of species included in the models is limited, consisting primarily of salmonids and almost entirely of species with a direct connection of the swim bladder to the oesophagus (physostomous), with the exception of walleye in the model of the hazard of external GBT. Laboratory studies of the effects of TDG supersaturation in fish that possess a physoclistous swimbladder (with no connection between the swim bladder and oesophagus and therefore unable to vent) exist (e.g. Bouck et al., 1976; Cornacchia & Colt, 1984; VanderKooi, Morris, Beeman, & Maule, 2003, see Appendix), but these did not meet the criteria for inclusion in our models.

4.7 | The scope of previous research

We identified 99 laboratory studies in which fish in freshwater were exposed to TDG supersaturation. Whereas these studies encompass a broad scope of outcomes and extrinsic and intrinsic factors, certain facets of GBT have been understudied, and others require additional study because of the experimental approaches previously taken.

Outcomes

We identified 25 categories of experimental outcomes that were reported as responses to exposure to TDG supersaturation, of which many were measured as sublethal effects. Unfortunately, some outcomes were generally only reported as qualitative data. We recommend that future studies focus on quantitative outcomes to improve objectivity in data collection and analysis, to generate reproducible results and to produce data that can be analysed statistically. In particular, we recommend additional quantitative studies of the impact of TDG on fish behaviour and blinded, quantitative histological studies of the impact of different levels of TDG on tissue damage in fish.

There are several outcomes that have received limited attention that could provide valuable insight into the effect of GBT on the survival of fish in the wild. For example, only four studies have explored the impacts of TDG on swimming performance in fish (e.g. Schiewe, 1974; Hans, Mesa, & Maule, 1999; Wang, An, Li, & Li, 2017; and Wang, Li, An, & Li, 2018). If bubbles are forming in the heart and occluding the gills during TDG exposure, we might expect reduced aerobic swimming capacity, affecting a fish's ability to capture prey, avoid predators and navigate in high flows, which could result in reduced fitness. For this reason, it is important for additional studies to quantify the effects of TDG on swimming performance in fish.

Other outcomes of interest include those that would elucidate the causes of mortality as a result of GBT. Multiple potential causes have been suggested, including bubbles blocking blood flow in the heart (Dawley, Schiewe, et al., 1976), the gills (Dawley, Schiewe, et al., 1976; Fidler, 1988; Stroud & Nebeker, 1976) or haemorrhages in the brain (Krise & Herman, 1989), and bubbles in the buccal cavity blocking water flow to the gills (Jensen, 1980). Causes may differ between durations of exposure to TDG supersaturation (Fidler, 1988) and life stages but knowing the mechanisms of mortality will likely facilitate predicting time to mortality.

Factors

Of the 22 different categories of factors that we identified in our review, one that stood out as particularly understudied was the relationship between locomotor activity and GBT. Exercise is known to exacerbate, reduce or have no effect on the symptoms of decompression sickness in humans during diving depending on the timing relative to decompression (Dujić et al., 2005; Jankowski, Tikuisis, & Nishi, 2004; Van Der Aue, Kellar, & Brinton, 1949). Because of similarities between decompression sickness and GBT, we might expect exercise to have similar effects on GBT. Thus far, only two studies have examined the effect of exercise on GBT in fish (Bouck et al., 1976; Grey et al., 1983) and these have revealed that the effects of activity on GBT vary with species and TDG level. If exercise exacerbates the effects of TDG supersaturation on fish, then most laboratory experiments, which have been carried out in static or low flow conditions, may not reveal the full extent of the effects GBT can have on wild fish, which may be more active and may experience more rapid water flows. Additional studies are necessary to describe the effects of exercise on GBT so that TDG guidelines are relevant for active fish in flowing water.

In addition, studies on species other than salmonids would improve our understanding of the effects of TDG on fish communities and the mechanisms by which TDG harms fish. Salmonids have been heavily studied because much of this research has been conducted in the Columbia River system and British Columbia, where there are many dams and where salmonids are economically, ecologically and culturally important. Keystone species that are restricted to shallow depths for a portion of their lifecycle would be important targets for future research. With a worldwide proliferation of dams underway (Zarfl et al., 2015), species that are important for commercial, recreational and subsistence fisheries in other parts of the world such as the Amazon, the Congo and the Mekong River Delta (Winemiller et al., 2016) warrant study. The only region outside of Canada and the United States where TDG research is being actively conducted is the Yangtze River system, where researchers are studying TDG effects on native species (Chen et al., 2012; Huang, Li, Du, & Li, 2010; Liang, Li, Li, & Tuo, 2013; Liu, Li, Jiang, & Wu, 2015; Liu, Li, Li, & Jiang, 2013). Species comparisons may also help to elucidate the mechanisms by which TDG harms fish. For example, additional comparisons between physostomes and physoclists could clarify the role of the swim bladder in GBT.

4.8 | Sources of bias

Many potential sources of bias assessed were found in the dataset of laboratory studies on GBT in fish (Figure 8). Having one or more of these potential sources of bias in a study does not mean the results are without scientific value. However, lack of rigour in the design and reporting of experimental studies can lead to biases in data collection and reporting. In the future, the design of TDG studies should include, whenever possible, random assignment of subjects to treatments, control groups and before-and-after designs, as well as treating, assessing and reporting all treatment groups in the same way to reduce the risk of biasing results.

In addition to the sources of bias assessed for the review, we observed multiple other oversights in study design and reporting that may reduce the accuracy and reproducibility of results used in our models. These include lack of information on TDG probe calibration and lack of information on measures taken to prevent bubbles from adhering to Weiss saturometers. Regular calibration of

the pressure sensors in Weiss saturometers is necessary for making accurate measurements but is rarely reported in the TDG literature. Describing calibration methods is outside the scope of this study, but we recommend the protocols described by Tanner and Johnson (2001). Bubbles adhere to the silastic tubing of Weiss saturometers when they are deployed above the compensation depth for bubble growth. Bubbles adhering to the silastic tubing of such probes tend to reduce the TDG readings. For this reason, our models are likely conservative estimates of the time to GBT outcomes at any given level of TDG supersaturation. To reduce bubble growth on the silastic tubing of Weiss saturometers in future experiments, we recommend deploying the probe below the compensation depth for bubble growth when possible, or using methods such as continuous shaking of the probe, deploying the probe in regions of high flow, or using a probe that is equipped with an impellor to mechanically remove bubbles, to ensure that measurements are accurate. Information on measures taken to reduce bubbles adhering to TDG probes should be reported in the methods of any reports or studies on TDG supersaturation.

4.9 | Application to field conditions

We recognize that our efforts focused exclusively on laboratory experiments. Data from laboratory experiments were used for this meta-analysis because these conditions can be carefully controlled; field studies incorporate fluctuating conditions and additional factors that increase variance in data and that is not easily modelled. To transfer results from laboratory studies to field applications, it is necessary to consider spatial and temporal variations in biotic and abiotic conditions, as well as important additional factors not included in this analysis, such as animal behaviour, interactions with other animals and additional stressors such as disease. We encourage future studies that combine laboratory and field components to fully understand the biological and ecological consequences of GBT on wild fish.

5 | CONCLUSIONS

By using a systematic approach, we were able to conduct a comprehensive search of the literature for laboratory studies of the effects of TDG supersaturation on freshwater fish, and by employing meta-analysis, we were able to develop models of the relationship between TDG supersaturation and GBT effects. These models can be used to estimate TDG effects on fish mortality and GBT symptoms, as well as their confidence intervals, for multiple species based on important intrinsic and extrinsic factors. In the literature, we identified that potential sublethal GBT effects are understudied, including quantitative assessments of the effects of TDG supersaturation on behaviour, tissue damage and swimming performance. Further study is also warranted on potential factors related to the severity and progression of GBT, such as species-specific differences among non-salmonids and the effects of exercise. Unfortunately, many of the GBT studies assessed had aspects of experimental design which increased their risk of bias; we encourage researchers to adopt the recommendations presented here to reduce the risk of bias by using best practices in experimental design.

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CONFLICT OF INTEREST

To the best of our knowledge, none of the authors have any conflict of interest that might influence their objectivity on the topic of this manuscript.

DATA AVAILABILITY STATEMENT

Data are available by contacting the corresponding author.

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REFERENCES

Antcliffe, B. L., Fidler, L. E., & Birtwell, I. K. (2002). *Effect of dissolved gas supersaturation on the survival and condition of juvenile rainbow trout (Oncorhynchus mykiss) under static and dynamic exposure scenarios*. Vancouver, British Columbia: Fisheries and Oceans Canada, Habitat and Enhancement Branch.

Antcliffe, B. L., Fidler, L. E., & Birtwell, I. K. (2003). *Lethal and sublethal responses of rainbow trout (Oncorhynchus mykiss) and coho (Oncorhynchus kisutch) fry to elevated dissolved gas supersaturation and temperature*. Vancouver, British Columbia: Fisheries & Oceans Canada, Habitat & Enhancement Branch.

Bates, D., Maechler, M., Bolker, B., & Walker, S. (2019). *Package 'lme4': Linear mixed-effects models using 'Eigen' and S4*. R package version 1.1-21. https://cran.r-project.org/web/packages/lme4/index.html

Bentley, W. W., Dawley, E. M., & Newcomb, T. W. (1976). Some effects of excess dissolved gas on squawfish, *Ptychocheilus oregonensis* (Richardson). In D. H. Fickeisen, & M. J. Schneider (Eds.), *Gas Bubble Disease* (pp. 41–46). Richland, Washington: Technical Information Center, Office of Public Affairs Energy Research and Development Administration.

Bouck, G. R., Nebeker, A. V., & Stevens, D. G. (1976). *Mortality, saltwater adaptation and reproduction of fish during gas supersaturation*. Duluth, Minnesota: US Environmental Protection Agency, Office of Research and Development, Environmental Research Laboratory.

Chen, S., Liu, X., Jiang, W., Li, K., Du, J., Shen, D., & Gong, Q. (2012). Effects of total dissolved gas supersaturated water on lethality and catalase activity of Chinese sucker (*Myxocyprinus asiaticus* Bleeker). *Journal of Zhejiang University Science B (Biomedecine & Biotechnology)*, *13*, 791–796. https://doi.org/10.1631/jzus.B1200022

Collins, A., Miller, J., Coughlin, D., & Kirk, S. (2014). *The production of quick scoping reviews and rapid evidence assessments a how to guide*.

Beta version 2. Retrieved September 9, 2014, from https://sbri.innovateuk.org/documents/3058188/3918930/The+Production+of+QSRs+and+REAs-+A+How+to+guide.pdf/45975020-be7d-4788-b74b-f3b6ed32c73a

Core Team, R. (2019). *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing. https://www.R-project.org/

Cornacchia, J. W., & Colt, J. E. (1984). The effects of dissolved gas supersaturation on larval striped bass, *Morone saxatilis* (Walbaum). *Journal of Fish Diseases*, *7*, 15–27. https://doi.org/10.1111/j.1365-2761.1984.tb00903.x

Counihan, T. D., Miller, A. I., Mesa, M. G., & Parsley, M. J. (1998). The effects of dissolved gas supersaturation on white sturgeon larvae. *Transactions of the American Fisheries Society*, *127*, 316–322. https://doi.org/10.1577/1548-8659(1998)127<0316:TEODGS>2.0.CO;2

Couto, T. B., & Olden, J. D. (2018). Global proliferation of small hydropower plants–science and policy. *Frontiers in Ecology and the Environment*, *16*, 91–100. https://doi.org/10.1002/fee.1746

Dawley, E. M., Blahm, T., Snyder, G., & Ebel, W. (1975). *Studies on Effects of Supersaturation of Dissolved Gases on Fish*. Seattle, Washington: US Department of Commerce, National Marine Fisheries Service.

Dawley, E. M., Monk, B. H., Schiewe, M. H., Ossiander, F., & Ebel, W. J. (1976). *Salmonid bioassay of supersaturated dissolved air in water. Ecological Research Series*, *413*. Duluth, Minnesota: US Environmental Protection Agency, Office of Research and Development, Environmental Research Laboratory.

Dawley, E. M., Schiewe, M., & Monk, B. (1976). Effects of long-term exposure to supersaturation of dissolved atmospheric gases on juvenile chinook salmon and steelhead trout in deep and shallow test tanks. In D. H. Fickeisen, & J. Schneider (Eds.), *Gas Bubble Disease* (pp. 1–20). Richland, Washington: Technical Information Center, Office of Public Affairs Energy Research and Development Administration.

Dujić, Ž., Palada, I., Obad, A., Duplančić, D., Baković, D., & Valic, Z. (2005). Exercise during a 3-min decompression stop reduces postdive venous gas bubbles. *Medicine and Science in Sports and Exercise*, *37*, 1319–1323. https://doi.org/10.1249/01.mss.0000174892.27331.ce

Ebel, W. J. (1971). *Dissolved Nitrogen Concentrations in the Columbia and Snake Rivers in 1970 and Their Effect on Chinook Salmon and Steelhead Trout*. Seattle, Washington: National Marine Fisheries Service.

Ebel, W. J., Dawley, E. M., & Monk, B. H. (1971). Thermal tolerance of juvenile Pacific salmon and steelhead trout in relation to supersaturation of nitrogen gas. *Fishery Bulletin*, *69*, 833–843.

Edsall, D. A., & Smith, C. E. (1991). Oxygen-induced gas bubble disease in rainbow trout, I (Walbaum). *Aquaculture and Fisheries Management*, *22*, 135–140.

Espmark, Å. M., Hjelde, K., & Baeverfjord, G. (2010). Development of gas bubble disease in juvenile Atlantic salmon exposed to water supersaturated with oxygen. *Aquaculture*, *306*(1), 198–204. https://doi.org/10.1016/j.aquaculture.2010.05.001

Fickeisen, D. H., & Montgomery, J. C. (1978). Tolerances of fishes to dissolved gas supersaturation in deep tank bioassays. *Transactions of the American Fisheries Society*, *107*, 376–381. https://doi.org/10.1577/1548-8659(1978)107<376:TOFTDG>2.0.CO;2

Fickeisen, D. H., Montgomery, J. C., & Hanf, R. W. Jr (1974). Effect of temperature on tolerance to dissolved gas supersaturation of black bullhead, *Ictalurus melas*. In D. H. Fickeisen, & J. Schneider (Eds.), *Gas Bubble Disease* (pp. 72–74). Richland, Washington: Technical Information Center, Office of Public Affairs Energy Research and Development Administration.

Fidler, L. E. (1988). *Gas bubble trauma in fish (Doctoral dissertation)*. Retrieved from, https://circle.ubc.ca/bitstream/id/97501/UBC_1988_A1

Fidler, L. E. (1998). *Laboratory Physiology Studies for Configuring and Calibrating the Dynamic Gas Bubble Trauma Mortality Model*. Montana: Kalispell.

Fidler, L. E., & Miller, S. B. (1994). *British Columbia water quality guidelines for dissolved gas supersaturation*. Retrieved from, http://www.env.gov.bc.ca/wat/wq/BCguidelines/tgp/index.html#TopOfPage

Gale, W. L., Maule, A. G., Postera, A., & Peters, M. H. (2004). Acute exposure to gas-supersaturated water does not affect reproductive success of female adult chinook salmon late in maturation. *River Research and Applications*, *20*, 565–576. https://doi.org/10.1002/rra.766

Geist, D. R., Linley, T. J., Cullinan, V., & Deng, Z. Q. (2013). Effects of total dissolved gas on chum salmon fry survival, growth, gas bubble disease, and seawater tolerance. *North American Journal of Fisheries Management*, *33*, 200–215. https://doi.org/10.1080/02755947.2012.750634

Gorham, F. P. (1898). Some physiological effects of reduced pressure on fish. *Journal of the Boston Society of Medicine*, *3*, 250–254.

Gorham, F. P. (1901). The gas-bubble disease of fish and its cause. *Bulletin of the United States Fish Commission*, *19*, 33–37.

Gray, R. H., Page, T. L., & Bronzi, P. (1982). Comparative tolerance to gas supersaturated water of carp, from the U. S. A. and Italy. *Journal of Fish Biology*, *20*, 223–227.

Gray, R. H., Page, T. L., Saroglia, M. G., & Festa, V. (1983). Tolerance of carp *Cyprinus carpio* and black bullhead *Ictalurus melas* to gas-supersaturated water under lotic and lentic conditions. *Environmental Pollution (Series A)*, *30*, 125–133. https://doi.org/10.1016/0143-1471(83)90009-0

Grill, G., Lehner, B., Thieme, M., Geenen, B., Tickner, D., Antonelli, F., … Zarfl, C. (2019). Mapping the world's free-flowing rivers. *Nature*, *569*(7755), 215–221. https://doi.org/10.1038/s41586-019-1111-9

Haddaway, N. R., Woodcock, P., Macura, B., & Collins, A. (2015). Making literature reviews more reliable through application of lessons from systematic reviews. *Conservation Biology*, *29*, 1596–1605. https://doi.org/10.1111/cobi.12541

Hans, K. M., Mesa, M. G., & Maule, A. G. (1999). Rate of disappearance of gas bubble trauma signs in juvenile salmonids. *Journal of Aquatic Animal Health*, *11*, 383–390. https://doi.org/10.1577/1548-8667(1999)011<0383:RODOGB>2.0.CO;2

Huang, X., Li, K., Du, J., & Li, R. (2010). Effects of gas supersaturation on lethality and avoidance responses in juvenile rock carp (*Procypris rabaudi* Tchang). *Journal of Zhejiang University-Science B*, *11*, 806–811. https://doi.org/10.1631/jzus.B1000006

International Commission On Large Dams (2018). *General synthesis*. Retrieved May 9, 2019, from https://www.icold-cigb.org/GB/world_register/general_synthesis.asp

Jankowski, L. W., Tikuisis, P., & Nishi, R. Y. (2004). Exercise effects during diving and decompression on postdive venous gas emboli. *Aviation, Space, and Environmental Medicine*, *75*, 489–496.

Jensen, J. O. T. (1980). *Effect of total gas pressure, temperature, and total water hardness in steelhead eggs and alevins*. In Proceedings of the Thirty-First Annual Northwest Fish Culture Conference (pp. 15–22). Courtenay, British Columbia.

Jensen, J. O. T. (1988). Combined effects of gas supersaturation and dissolved oxygen levels on steelhead trout (*Salmo gairdneri*) eggs, larvae, and fry. *Aquaculture*, *68*, 131–139. https://doi.org/10.1016/0044-8486(88)90236-0

Jensen, J. O. T., Schnute, J., & Alderdice, D. F. (1986). Assessing juvenile salmonid response to gas supersaturation using a general multivariate dose-response model. *Canadian Journal of Fisheries and Aquatic Sciences*, *43*, 1694–1709. https://doi.org/10.1139/f86-213

Krise, W. F., & Herman, R. L. (1989). Tolerance of lake trout, *Salvelinus namaycush* (Walbaum), sac fry to dissolved gas supersaturation. *Journal of Fish Diseases*, *12*, 269–273. https://doi.org/10.1111/j.1365-2761.1989.tb00312.x

Krise, W. F., & Herman, R. L. (1991). Resistance of underyearling and yearling Atlantic salmon and lake trout to supersaturation with air. *Journal of Aquatic Animal Health*, *3*, 248–253. https://doi.org/10.1577/1548-8667(1991)003<0248:ROUAYA>2.3.CO;2

Krise, W. F., Meade, J. W., & Smith, R. A. (1990). Effect of feeding rate and gas supersaturation on survival and growth of lake trout. *The Progressive Fish-Culturist*, *52*, 45–50. https://doi.org/10.1577/1548-8640(1990)052<0045:EOFRAG>2.3.CO;2

Liang, R., Li, B., Li, K., & Tuo, Y. (2013). Effect of total dissolved gas supersaturated water on early life of David's schizothoracin (*Schizothorax davidi*). *Journal of Zhejiang University-Science B*, *14*, 632–639. https://doi.org/10.1631/jzus.B1200364

Liu, X., Li, K., Jiang, W., & Wu, S. (2015). Biochemical responses and survival of rock carp (*Procypris rabaudi*) to total dissolved gas supersaturated water. *Ichthyological Research*, *62*, 171–176. https://doi.org/10.1007/s10228-014-0420-0

Liu, X., Li, K., Li, R., & Jiang, W. (2013). Effect of chronic and acute exposure to total dissolved gas supersaturation on growth and survival in juvenile rock carp (*Procypris rabaudi* Tchang). *Journal of Food, Agriculture and Environment*, *11*, 1390–1393.

Lund, M., & Heggberget, T. G. (1985). Avoidance response of two-year-old rainbow trout, *Salmo gairdneri* R., to air-supersaturated water: Hydrostatic compensation. *The Journal of Fish Biology*, *26*, 193–200.

Machado, J. P., Garling, D. L. Jr, Kevern, N. R., Trapp, A. L., & Bell, T. G. (1987). Histopathology and the pathogenesis of embolism (gas bubble disease) in rainbow trout (*Salmo gairdneri*). *Canadian Journal of Fisheries and Aquatic Sciences*, *44*, 1985–1994.

Maule, A. G., Beeman, J. W., Hans, K. M., Mesa, M. G., Haner, P., & Warren, J. J. (1997). *Gas Bubble Disease Monitoring and Research of Juvenile Salmonids: Annual Report 1996 (No. DOE/BP-93279-1)*. Portland, Oregon: Bonneville Power Administration; Geological Survey, Columbia River Research Lab.

Maynard, C. (2008). *Evaluation of total dissolved gas criteria (TDG) biological effects research: A literature review*. Washington State Department of Ecology Water Quality Program (Publication Number 08–10-059).

Mcintyre, P. B., Reidy, C. A., & Revenga, C. (2016). Linking freshwater fishery management to global food security and biodiversity conservation. *PNAS*, *113*, 12880–12885. https://doi.org/10.1073/pnas.1521540113

Meekin, T. K., & Allen, R. L. (1974). Summer chinook and sockeye salmon mortality in the upper Columbia River and its relation to nitrogen supersaturation. *Washington Department of Fisheries Technical Report*, *12*, 127–153.

Mesa, M. G., Weiland, L. K., & Maule, A. G. (2000). Progression and severity of gas bubble trauma in juvenile salmonids. *Transactions of the American Fisheries Society*, *129*, 174–185. https://doi.org/10.1577/1548-8659(2000)129<0174

Muggeo, V. M. R. (2019). *segmented: Regression models with break-points / change-points estimation*. R package version 1.1-0. https://cran.r-project.org/web/packages/segmented/index.html

Nebeker, A. V., Andros, J. D., McCrady, J. K., & Stevens, D. G. (1978). Survival of steelhead trout (*Salmo gairdneri*) eggs, embryos, and fry in air-supersaturated water. *Journal of the Fisheries Research Board of Canada*, *35*, 261–264. https://doi.org/10.1139/f78-043

Nebeker, A. V., Bouck, G. R., & Stevens, D. G. (1976). Carbon dioxide and oxygen-nitrogen ratios as factors affecting salmon survival in air-supersaturated water. *Transactions of the American Fisheries Society*, *105*, 425–429. https://doi.org/10.1577/1548-8659(1976)105<425:CDAORA>2.0.CO;2

Nebeker, A. V., Hauck, K. A., & Baker, F. D. (1979). Temperature and oxygen-nitrogen gas ratios affect fish survival in air-supersaturated water. *Water Research*, *13*, 299–303. https://doi.org/10.1016/0043-1354(79)90210-0

Newcomb, T. W. (1978). *Some physiological effects of total gas pressure supersaturated water on juvenile Pacific salmon and steelhead trout: A laboratory and field study (Doctoral dissertation)*. Suzzallo and Allen Libraries: University of Washington, Seattle.

Oregon Department of Environmental Quality & Washington State Department of Ecology. (2009). *Adaptive management team total dissolved gas in the Columbia and Snake Rivers: Evaluation of the 115 percent total dissolved gas forebay requirement*. (Publication no. 09–10-002).

Pickett, P. J., & Harding, R. (2002). *Total maximum daily load (TMDL) for Lower Columbia River total dissolved gas*. Oregon Department of Environmental Quality & Washington State Department of Ecology (Publication no. 02–03-004).

Pleizier, N. K., Nelson, C., Cooke, S. J., & Brauner, C. J. (2020). Understanding gas bubble trauma in an era of hydropower expansion: How do fish compensate at depth? *Canadian Journal of Fisheries and Aquatic Sciences*, *77*, 556–563. https://doi.org/10.1139/cjfas-2019-0243

Rucker, R. R. (1975). Gas-bubble disease: Mortalities of coho salmon, *Oncorhynchus kisutch*, in water with constant total gas pressure and different oxygen-nitrogen ratios. *Fishery Bulletin*, *73*, 915–918.

Ryan, B. A., & Dawley, E. M. (1998). *Effects of dissolved gas supersaturation on fish residing in the Snake and Columbia Rivers, 1997*. Seattle, Washington: Bonneville Power Administration.

Schiewe, M. H. (1974). Influence of dissolved atmospheric gas on swimming performance of juvenile chinook salmon. *Transactions of the American Fisheries Society*, *103*, 717–721. https://doi.org/10.1577/1548-8659(1974)103<717:IODAGO>2.0.CO;2

Schisler, G. J., Bergersen, E. P., & Walker, P. G. (2000). Effects of multiple stressors on morbidity and mortality of fingerling rainbow trout infected with *Myxobolus cerebralis*. *Transactions of the American Fisheries Society*, *129*, 859–865. https://doi.org/10.1577/1548-8659(2000)129<0859:EOMSOM>2.3.CO;2

Schneider, M. J. (2008). *Washington and Oregon State - Adaptive Management Team Resident Fish Literature Review* (pp. 1–37).

Shrank, B. P., Dawley, E. M., & Ryan, B. (1997). *Evaluation of the effects of dissolved gas supersaturation on fish and invertebrates in Priest Rapids Reservoir, and downstream from Bonneville and Ice Harbor Dams, 1995*. Seattle, Washington: Coastal Zone and Estuarine Studies Division, Northwest Fisheries Science Center, National Marine Fisheries Service.

Shrimpton, J. M., Randall, D. J., & Fidler, L. E. (1990a). Assessing the effects of positive buoyancy on rainbow trout (*Oncorhynchus mykiss*) held in gas supersaturated water. *Canadian Journal of Zoology*, *68*, 969–973.

Shrimpton, J. M., Randall, D. J., & Fidler, L. E. (1990b). Factors affecting swim bladder volume in rainbow trout (*Oncorhynchus mykiss*) held in gas supersaturated water. *Canadian Journal of Zoology*, *68*, 962–968.

Stroud, R. K., Bouck, G. R., & Nebeker, A. V. (1975). Pathology of acute and chronic exposure of salmonid fishes to supersaturated water. In W. A. Adams (Ed.), *Chemistry and Physics of Aqueous Gas Solutions* (pp. 435–449). Princeton, New Jersey: Electrothermics and Metallurgy and Industrial Electrolytic Divisions, Electrochemical Society.

Stroud, R. K., & Nebeker, A. V. (1976). A study of the pathogenesis of gas bubble disease in steelhead trout (*Salmo gairdneri*). In D. H. Fickeisen, & M. J. Schneider (Eds.), *Gas Bubble Disease* (pp. 66–71). Richland, Washington: Technical Information Center, Office of Public Affairs Energy Research and Development Administration.

Tanner, D. Q., & Johnston, M. W. (2001). *Data-collection methods, quality assurance data, and site considerations for total dissolved gas monitoring, lower Columbia River, Oregon and Washington, 2000*. Oregon Water Resources Department, Portland. Investigation Report 01-4005, pp. 1–19.

The Cochrane Collaboration. (2011). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. Retrieved September 9, 2016, from www.handbook.cochrane.org

Therneau, T. M. (2019a). *coxme: Mixed effects Cox models*. R package version 2.2-14. https://CRAN.R-project.org/package=coxme

Therneau, T. M. (2019b). *survival: Survival analysis. R package version 3.1-8*. https://CRAN.R-project.org/package=survival

UK Civil Service (2010). *Rapid evidence assessment toolkit index*. Retrieved September 9, 2016, from http://webarchive.nationalarchives.gov.uk/20140305122816/http://www.civilservice.gov.uk/networks/gsr/resources-and-guidance/rapid-evidence-assessment

US National Marine Fisheries Service (2000). *Endangered species act - section 7 consultation, biological opinion: Reinitiation of consultation on operation of the federal Columbia River power system, including the juvenile fish transportation program, and 19 bureau of reclamation projects in the Columbia Basin*. Seattle, Washington.

Van Der Aue, O. E., Kellar, R. J., & Brinton, E. S. (1949). *The effect of exercise during decompression from increased barometric pressures on the incidence of decompression sickness in man (No. NEDU 8–49)*. Panama City, FL: Navy Experimental Diving Unit Washington DC.

VanderKooi, S. P., Morris, R. G., Beeman, J. W., & Maule, A. G. (2003). *Chapter II: The progression and lethality of gas bubble disease in resident fish of Rufus Woods Lake*. Cook, Washington. Retrieved from http://wfrc.usgs.gov/publications/reportpdf/usgsfrgbdgrandcouleedam.pdf

Wang, Y., An, R., Li, Y., & Li, K. (2017). Swimming performance of rock carp *Procypris rabaudi* and prenant's schizothoracin *Schizothorax prenanti* acclimated to total dissolved gas supersaturated water. *North American Journal of Fisheries Management*, *37*(6), 1183–1190. https://doi.org/10.1080/02755947.2017.1353558

Wang, Y., Li, K., Li, J., Li, R., & Deng, Y. (2015). Tolerance and avoidance characteristics of Prenant's schizothoracin *Schizothorax prenanti* to total dissolved gas supersaturated water. *North American Journal of Fisheries Management*, *35*(4), 827–834. https://doi.org/10.1080/02755947.2015.1052160

Wang, Y., Li, Y., An, R., & Li, K. (2018). Effects of total dissolved gas supersaturation on the swimming performance of two endemic fish species in the Upper Yangtze River. *Scientific Reports*, *8*(10063), 1–9. https://doi.org/10.1038/s41598-018-28360-7

Wang, Y., Liang, R., Tuo, Y., Li, K., & Hodges, B. (2015). Tolerance and avoidance behavior towards gas supersaturation in rock carp *Procypris rabaudi* with a history of previous exposure. *North American Journal of Aquaculture*, *77*(4), 478–484. https://doi.org/10.1080/15222055.2015.1059913

Weitkamp, D. E. (2008). *Total Dissolved Gas Supersaturation Biological Effects, Review of Literature 1980–2007*. Bellevue, Washington: Parametrix.

White, R. G., Phillips, G., Liknes, G., Prammer, J., Conner, W., Fidler, L. E., … Dwyer, W. (1991). *Effects of supersaturation of dissolved gases on the fisher of the Bighorn River downstream of the Yellowtail Afterbay Dam*. U.S. Fish and Wildlife Service, Montana Cooperative Fishery Research Unit & Montana Department of Fish, Wildlife, and Parks.

Winemiller, K. O., McIntyre, P. B., Castello, L., Fluet-Chouinard, E., Giarrizzo, T., Nam, S., … Sáenz, L. (2016). Balancing hydropower and biodiversity in the Amazon, Congo, and Mekong. *Science*, *351*(6269), 128–129. https://doi.org/10.1126/science.aac7082

Zarfl, C., Lumsdon, A. E., Berlekamp, J., Tydecks, L., & Tockner, K. (2015). A global boom in hydropower dam construction. *Aquatic Sciences*, *77*, 161–170. https://doi.org/10.1007/s00027-014-0377-0

SUPPORTING INFORMATION

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

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