Harmful Algae 82 (2019) 73–81

Contents lists available at ScienceDirect

Harmful Algae

journal homepage: www.elsevier.com/locate/hal

Neurological illnesses associated with Florida red tide (*Karenia brevis*) blooms

Roberto Efrain Diaz[a,1,2], Melissa A. Friedman[b], Di Jin[c], Andrew Beet[c], Barbara Kirkpatrick[d,e], Andrew Reich[f], Gary Kirkpatrick[e], Steven G. Ullmann[a,*], Lora E. Fleming[d,g], Porter Hoagland[c]

[a] Department of Health Management and Policy, University of Miami, Coral Gables, FL, USA
[b] Mount Sinai Medical Center, Miami Beach, FL, USA
[c] Marine Policy Center, Woods Hole Oceanographic Institution, Woods Hole, MA, USA
[d] Department of Epidemiology and Public Health, Miller School of Medicine, University of Miami, Miami, FL, USA
[e] Mote Marine Laboratory, Sarasota, FL, USA
[f] Aquatic Toxins Program, Bureau of Epidemiology, Florida Department of Health, Tallahassee, FL, USA
[g] European Centre for Environment and Human Health, University of Exeter Medical School, Truro, Cornwall, UK

ARTICLE INFO

Keywords:
Karenia brevis (*K. brevis*)
brevetoxin
headache
exposure-response
illness cost

ABSTRACT

Human respiratory and gastrointestinal illnesses can result from exposures to brevetoxins originating from coastal Florida red tide blooms, comprising the marine alga *Karenia brevis* (*K. brevis*). Only limited research on the extent of human health risks and illness costs due to *K. brevis* blooms has been undertaken to date. Because brevetoxins are known neurotoxins that are able to cross the blood-brain barrier, it is possible that exposure to brevetoxins may be associated with neurological illnesses. This study explored whether *K. brevis* blooms may be associated with increases in the numbers of emergency department visits for neurological illness. An exposure-response framework was applied to test the effects of *K. brevis* blooms on human health, using secondary data from diverse sources. After controlling for resident population, seasonal and annual effects, significant increases in emergency department visits were found specifically for headache (ICD-9 784.0) as a primary diagnosis during proximate coastal *K. brevis* blooms. In particular, an increased risk for older residents (≥55 years) was identified in the coastal communities of six southwest Florida counties during *K. brevis* bloom events. The incidence of headache associated with *K. brevis* blooms showed a small but increasing association with *K. brevis* cell densities. Rough estimates of the costs of this illness were developed for hypothetical bloom occurrences.

1. Introduction

Blooms of the marine alga *Karenia brevis (K. brevis)* occur regularly along the coast of the Gulf of Mexico from southeast Texas to southwest Florida. Despite their designation as “red tides,” *K. brevis* blooms are typically colorless but occasionally may be characterized by a distinct brown color. At moderate to high densities, *K. brevis* blooms can be harmful to humans and marine life because the algae produce potent natural neurotoxins called brevetoxins (Fleming et al., 2011).

Brevetoxins can cause morbidity in humans and morbidity or mortality in marine mammals, seabirds, and other marine organisms (Fleming et al., 2011; Watkins et al., 2008). The human consumption of shellfish contaminated with brevetoxins causes an illness known as neurotoxic shellfish poisoning (NSP) (Reich et al., 2015; Watkins et al., 2008). The inhalation of brevetoxins aerosolized during coastal blooms has been associated with human respiratory illness, particularly asthma, bronchitis, and chronic obstructive pulmonary disease (Cheng et al., 2005; Fleming et al., 2009, 2011). These blooms may also lead to the closure of shellfish beds and reduced sales in local businesses, such as those that cater to tourists (Adams et al., 2002; Habas and Gilbert, 1975; Larkin and Adams, 2007; Morgan et al., 2009, 2010).

Over the past two decades, several studies have highlighted the adverse human health risks and consequent economic effects associated with Florida red tide blooms (Adams et al., 2018; Hoagland et al., 2002). Human brevetoxin exposures and their health impacts may range in severity, but generally lead to increases in: the purchase of

* Corresponding author at: Department of Health Management and Policy, University of Miami, 5250 University Drive, Jenkins Building 421B, Coral Gables, FL, USA.

E-mail address: sullmann@bus.miami.edu (S.G. Ullmann).

[1] Current Address: Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco, CA, USA.

[2] Tetrad Graduate Program, University of California, San Francisco, San Francisco, CA, USA.

https://doi.org/10.1016/j.hal.2018.07.002
Received 6 March 2018; Received in revised form 7 July 2018; Accepted 7 July 2018
1568-9883/

over-the-counter medications; self-treatment by asthmatics with prescription drugs; visits to outpatient clinics, doctors, or emergency departments; and hospital inpatient admissions. During active Florida red tide blooms, Fleming et al. (2005a, 2005b, 2011; Bean et al., 2011) found that brevetoxin aerosols could exacerbate asthma or other respiratory conditions with acute and sub-chronic sequelae. Kirkpatrick et al. (2006, 2009) identified increased visits to a hospital emergency department in Sarasota, Florida associated with red tide blooms for a range of respiratory and digestive illnesses.

Hoagland et al. (2009) used an exposure-response framework to estimate the potential economic effects of *K. brevis* blooms on Florida emergency department visits to a single hospital for respiratory illnesses during 2001–06. These authors found that subsequent hospital emergency department visits could be explained by cell counts from the previous week, when controlling for local air temperatures, regional influenza outbreaks, regional pollen counts, and a local measure of tourist visits. The 1-week lag was explained by the duration of each of the following events: a delay between observances of live *K. brevis* cells, the release of the toxin as the algal cells lysed after death, the movement of the toxin from the water column to the atmosphere through physical aerosolization, the eventual human inhalation of and reaction to the toxin, and the delay in seeking medical care. In a follow-up study, Hoagland et al. (2014) found an association between *K. brevis* blooms and increases in the number of emergency department visits and hospital inpatient admissions for both respiratory and digestive illnesses. After controlling for resident population (a proxy for tourism), seasonal and annual effects, red tide blooms were associated with these adverse health effects, particularly in older cohorts (≥55 years) located in six southwest coastal counties in Florida.

Many harmful algae bloom (HAB) toxins (e.g., brevetoxin, ciguatoxin, saxitoxin, domoic acid), target human and animal neurological systems (Friedman and Levin, 2005; Friedman et al., 2017). Human consumption of ciguatoxin in contaminated fish, for instance, is associated with memory complaints, headache, fatigue, anxiety, depression, and diverse paresthesias (Arena et al., 2004; Friedman and Levin, 2005; Friedman et al., 2007, 2017), lasting from days to years (Fleming et al., 2002). Often, cardiovascular, gastrointestinal, and neurological symptoms present together in patients suffering from different types of HAB poisonings, such as NSP (brevetoxin) or ciguatera fish poisoning (CFP; ciguatoxin) (Friedman et al., 2008, 2017; McFarren et al., 1965).

Brevetoxins are released from *K. brevis* cells and bind to voltage-gated sodium channels in neurons. Chemically similar to ciguatoxins, brevetoxins are lipophilic cyclic polyethers that pass through biological membranes readily—including the blood-brain barrier and the placenta, allowing them to disturb diverse neuronal processes in humans and animals (Benson et al., 2006, Fleming et al., 2011; Friedman et al., 2017). Upon the consumption of contaminated seafood, such as shellfish and possibly finfish, brevetoxins can cause acute neurologic illness with symptoms ranging from paresthesias to coma (Watkins et al., 2008). Beyond individual cases and case clusters of NSP, however, there has been very little research into the potential population-level effects of brevetoxins on emergency department visits or hospital admissions for neurologic illness (Reich et al., 2015).

Neurological symptoms such as headaches, dysesthesia, or paresthesia can have significant effects on the ability of humans to function normally. The personal impacts of such pain can be problematic to evaluate, as they are influenced by the ability of each individual to tolerate symptoms of varying severity and/or frequency (Pizzo and Clark, 2011). Neurological illnesses may also lead to anxiety or depression, lost career or educational opportunities, as well as emotional or psychological impacts on immediate family members or even on broader social networks (Stovner and Andrée, 2008).

Aside from personal suffering, neurological illnesses are known to impose significant economic effects, comprising the costs of medical treatments and lost productivity, either through work absences (absenteeism) or reduced performance at work (presenteeism). A 2010 study by Olesen et al. (2012) of the economic costs of all brain illnesses in Europe estimated annual costs of more than $1 trillion. All monetary figures in this study were adjusted to 2017 dollars using the U.S.consumer price index (BLS, 2017). A 2002 U.S.study found that headaches were the most common type of neurological illness, leading to an estimate of lost productivity of $27 billion per year, attributed mostly (~80%) to reduced performance at work (Stewart et al., 2003). A separate U.S.study based on data compiled through the 2008 Medical Expenditure Panel Survey estimated direct medical expenditures for headache illnesses to be $7.5 billion per year in the United States (Pizzo and Clark, 2011). In the European study cited above, headaches (including migraines, tension-type, and others) were found to be the most common brain illness, although the estimated economic cost per patient (about $430/year) of headache was found to be lower than the costs of other brain illnesses (Olesen et al., 2012). Elston Lafata et al. (2004) estimated that migraine, a type of severe headache, led on average to $900/year in additional total medical expenditures per patient relative to the average expenditure for all participants in a surveyed health plan.

This paper explores the hypothesis that near coastal occurrences of *K. brevis* blooms could lead to increases in the incidence of human neurological illnesses. Panel data on monthly emergency department visits were compiled and analyzed for the incidence of neurological illness in the coastal fringes of six counties in southwest Florida over the 5-year period from 2005-09. These data were matched to monthly data on *K. brevis* cell counts proximate to these counties over the same period. The study revealed a relationship between Florida red tide events and a primary diagnosis of headache in emergency department visits of individuals ≥55 years. Although the observed incidence of headache in this cohort was small, headache frequency was linked significantly to the density of cells in nearby *K. brevis* blooms. This study also presents estimates of the approximate scale of the economic costs of headache as a form of neurological illness resulting from Florida red tides. Included in the Discussion is an argument for why these findings are likely to be conservative, therefore necessitating further investigation. Some recommendations for researchers and guidance for medical practitioners are provided in the Conclusions.

2. Material and Methods

2.1. Measures of Florida red tide bloom events

Measures of Florida red tide blooms were compiled using counts of *K. brevis* cells obtained through opportunistic water sampling efforts along the Florida Gulf coast during the study period. These included all *K. brevis* counts greater than 10^3 cell counts/L within 15 km of waters proximate to the following six counties (from north to south) on the Southwest Florida coast: Pinellas, Hillsborough, Manatee, Sarasota, Charlotte, and Lee (FWRI, 2013). Zeros were assigned to months for average counts below 10^3 cell counts/L or when no water samples were taken. Because water sampling was not carried out consistently over either time or area, the maximum cell count in a month and county was taken to represent temporal or spatial bloom severity (Fig. 1, Supp. Fig. 1). Geographic Information Systems (GIS) data for Florida counties and ZIP codes were mapped using QGIS v2.18.20 and the geographic coordinate system North American 1983 Datum/Florida GDL Albers (QGIS Development Team, 2018). Florida county and ZIP code shape files were downloaded via the Florida Geographic Data Library at (http://www.fgdl.org/metadataexplorer/explorer.jsp).

2.2. Emergency department visit data

Human neurological health risks related to Florida red tide blooms were explored using a subset of neurological diagnoses thought to be associated with brevetoxin exposure resulting in emergency department visits. Data on emergency department visits during 2005-09 were

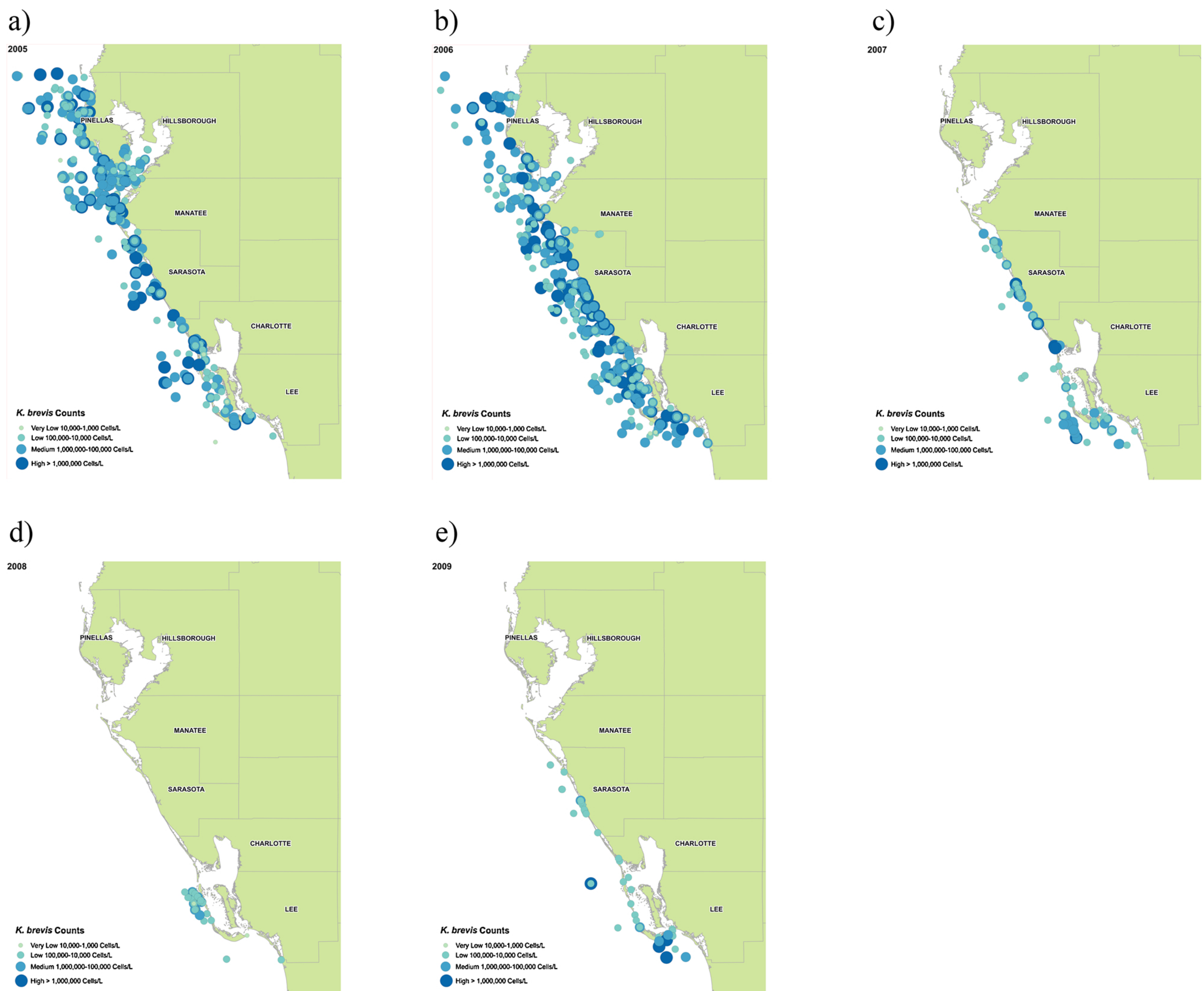

Fig. 1. Annual maps of *K. brevis* blooms (2005-09).
Distributions and cell densities of Florida red tide (*K. brevis*) blooms along the southwest Florida coast during the study period. A monthly time-lapse video from January 2005-December 2009 is available in the Supplement (Supp. Fig. 1).

obtained from the Florida Agency for Health Care Administration (AHCA). The AHCA data consist of a set of annual files, each containing approximately 1.5 million patient records, representing individual emergency department visits. Due to changing data formats over time, these files comprised anywhere from 65-101 distinct variables. For the purpose of this study, only five variables were compiled for each patient: visit date (begindate); county of the medical facility attended (fac_county); age at the time of the visit (age); principal diagnosis code (prindiag); and ZIP code of permanent residence (zipcode). Patients with non-Florida ZIP codes (i.e., outside the range of 32000-35000) were assumed to be tourists. The final project database included emergency department records by age, location, and month for coastal residents located in county ZIP codes within 8 km of the coast and for county tourists (assumed to be visiting within 8 km of the coast) for the different types of neurological illness.

The primary diagnosis code for each patient using the International Classification of Diseases Version 9 (ICD-9) was used to identify the type of illness. The following ICD-9 codes were investigated initially to explore the potential effects of *K. brevis* blooms on neurological illnesses: diseases of the nervous system (ICD-9 320-359); diseases of the sense organs (ICD-9 360-389); diseases of the musculoskeletal system and connective tissue (ICD-9 710-739); symptoms, signs, and ill-defined conditions (ICD-9 780-799); and injury and poisoning (ICD-9 800-999). Illnesses for each individual comprised only the primary diagnoses. The emergency department visit data were linked to the *K. brevis* cell counts and other variables by month and by county, respectively, to create a data set for analysis (Fig. 2, Supp. Fig. 2).

2.3. Population and tourism data

Data on residential populations and a measure of tourism were compiled in order to control for the number of persons potentially exposed during a red tide. Annual population data by county were compiled for 2005-09 from the U.S. Census Bureau (BoC, 2013). Monthly data on the number of hotel and motel rooms occupied in each county were compiled for the same period (STR, 2013). Room occupancies were assumed to be a proxy for visits to coastal counties by tourists, including "snow-birds"—elderly individuals who reside in coastal Florida for extended periods during the winter months. The total numbers of tourists measured in this way would comprise an underestimate of non-resident tourist populations, because condominium rentals and time-shares are now a significant component of the coastal Florida housing market. In the absence of comprehensive data on condominium or time-share occupancies, monthly variations in these occupancies were assumed to match variations in hotel and motel room occupancies; and the latter were employed as a proxy for the monthly

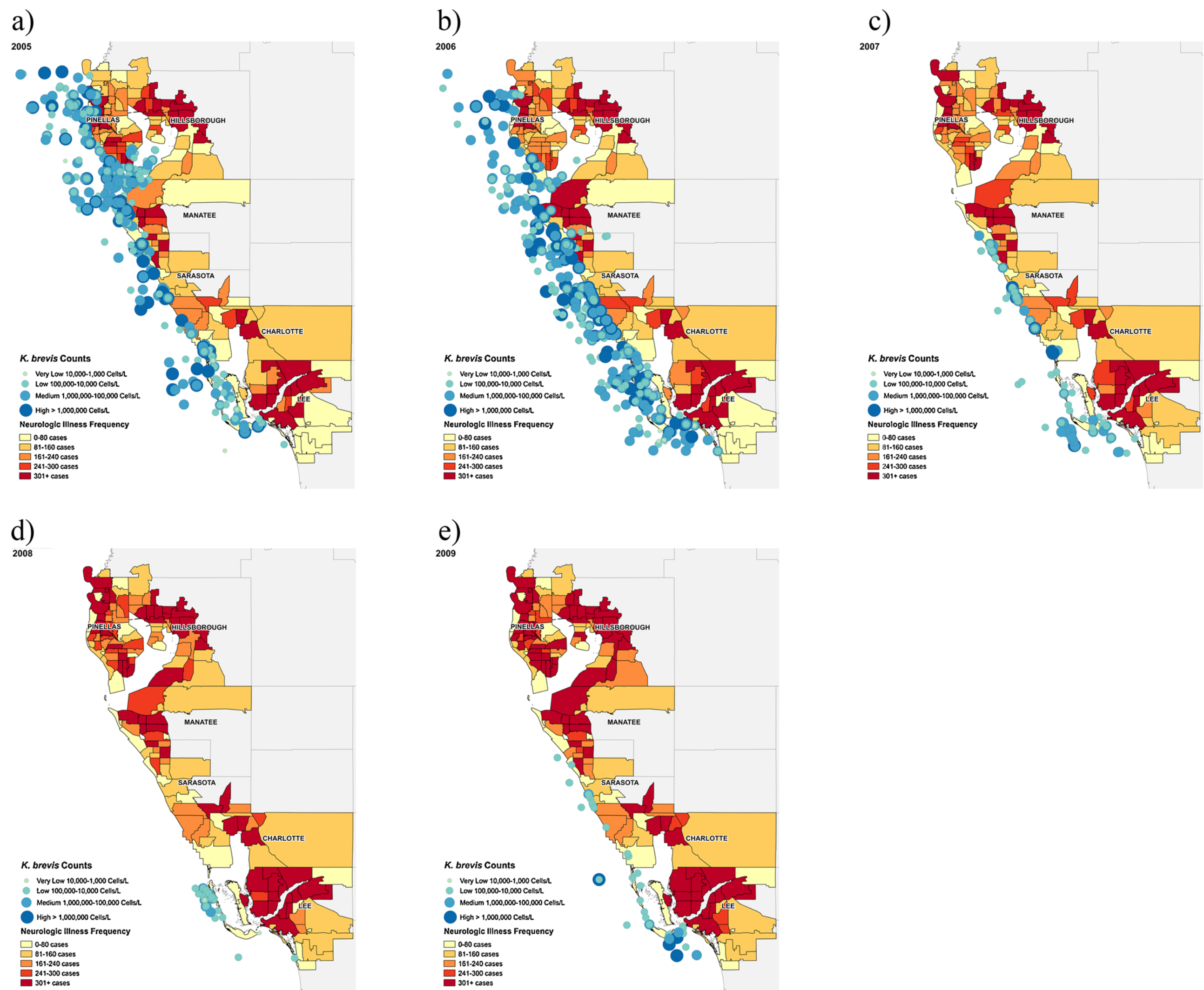

Fig. 2. Annual maps of neurologic illness frequency as a correlate of *K. brevis* blooms (2005-09).
Distributions and cell densities of Florida red tide (*K. brevis*) blooms along the southwest Florida coast during the study period. Onshore shapes depict the incidence of neurological illnesses of interest (as reported in Section 2.2) for persons of all ages in ZIP codes proximate to the coast. A monthly time-lapse video from January 2005-December 2009 is available in the Supplement (Supp. Fig. 2).

variability of tourist visits per county.

2.4. Model

Time-series cross-section regression models were developed using monthly data at the county level. Let y be the response (e.g., the number of visits to emergency department facilities per month in a county by residents of coastal communities and tourists). The relationship between the response and several covariates was modeled as follows, using a Da Silva variance-component, moving-average formulation:

$$y_{it} = \alpha_0 + \alpha_1 HAB_{it} + \alpha_2 pop_{it} + \alpha_3 tour_{it} + \sum_{j=1}^{J} B_j M_j + \sum_{k=1}^{K} \gamma_k Y_k + \alpha_i + b_t + \varepsilon_{it}$$

where i is the index for each of six individual counties, t is the index for month, α_0 is the intercept, HAB_{it} is a measure of HAB occurrence and severity in county i during month t; pop_{it} is the population in county i during month t; $tour_{it}$ is a measure of tourist visits (i.e., number of hotel and motel rooms occupied) in county i during month t; M_j is a categorical variable for month j; Y_k is a categorical variable for year k; a_i is a month-invariant county effect; b_t is a county-invariant time effect; and ε_{it} comprises a residual effect unaccounted for by the explanatory variables and the specific time and cross-sectional unit effects. α, β and γ are coefficients to be estimated. Thus, changes in y were modeled to reflect a combination of monthly and yearly fluctuations, HAB occurrences, and variations in county populations and the numbers of tourist visitors. Note that the monthly categorical variables were assumed to comprise the cumulative effects of other seasonal factors influencing visitation to a medical facility, such as cooler temperatures or the prevalence of flu outbreaks in the winter or high pollen counts in the spring or fall (*cf*. Hoagland et al., 2009).

2.5. Descriptive Statistics

To create a data set for analysis, the emergency department visitation data for neurological illnesses were merged with the model covariates by month and by county, respectively. The data set comprised 360 observations (5 years × 12 months × 6 counties). Descriptive statistics by county on emergency department visits for headache as a primary neurological illness diagnosis (ICD-9 784.0) for all patients and for patients aged 55 and older are summarized in Table 1. Note that, although the response (emergency department visits for a primary

Table 1
Descriptive statistics by county of Emergency Department (ED) visits and other predictors (Monthly averages, 2005-09).

Variable	Pinellas	Hillsborough	Manatee	Sarasota	Charlotte	Lee
Total ED Visits - Headache	48.55	46.88	10.35	14.88	10.13	30.38
ED Visits - Headache ≥ 55 years	10.32	6.83	2.72	4.65	2.48	6.77
% of Total ED Visits - Headache ≥ 55 years	21.3%	14.6%	26.3%	31.3%	24.5%	22.3%
Total Population (10^5 people)	9.42	11.77	3.13	3.84	1.62	5.98
Population ≥ 55 years (10^5 people)	3.20	2.62	1.06	1.65	0.73	2.05
% of Total Population ≥ 55 years	34.0%	22.3%	33.9%	42.9%	45.2%	34.3%
Tourism (10^4 rooms)	32.81	38.22	6.28	8.88	1.55	18.52
K. brevis Cell Counts (10^7 cell counts/L)	0.06	0.06	0.16	1.26	0.05	0.30

diagnosis of headache) was age-restricted, the measures comprising county resident populations and room occupancies were not. The county rankings, from most to least, of residents and room occupancies are identical: Hillsborough, Pinellas, Lee, Sarasota, Manatee, and Charlotte. From 35-45% of the total populations in Pinellas, Manatee, Sarasota, Charlotte, and Lee counties were aged 55 and over.

Across the six counties, the emergency department visits for headache ranged from 0 to 17 per month (Table 2), but all counties averaged less than 11 emergency department visits of that type per month (Table 1). By county, patients aged 55 and older accounted for between 14-29% of the total numbers of emergency department visits with a primary diagnosis of headache. The average number of emergency department visits from patients living outside the coastal region was a relatively small proportion of the total, ranging from 0-3 visits per month (data not shown). Regionally, the measure of *K. brevis* blooms (maximum monthly cell count) ranged from 0 to 16.2×10^7 cell counts/L (Table 2), but monthly averages varied across the six counties in the study area, with Sarasota and Lee counties showing the highest such averages (Table 1).

3. Results

3.1. Exposure-response

A number of model formulations comprising alternative measures of the response were explored initially. The response, representing the number of monthly emergency department visits in a county for neurological illnesses by residents and tourists located within 8 km of the seashore, was compiled in different ways to examine the presence of possible effects both by age cohort (≤17, 18–54, ≥55 years) and by ICD-9 neurological illness type. The results of one formulation, finding a significant effect of *K. brevis* blooms on the incidence of headache in older cohorts, are reported here; the results of alternative formulations are available from the authors upon request.

Table 3 presents the Da Silva regression results for a response measuring a primary diagnosis of headache (ICD-9 784.0) in the older

Table 2
Descriptive statistics of Emergency Department (ED) visits and other predictors across counties (Monthly averages, 2005-09).

Emergency Department Visits (2005-09)				
Variable	Mean	S.D.	Min.	Max.
Total ED Visits - Headache*	5.63	3.75	0	17
Population (10^5 people)	5.96	3.59	1.54	12.01
Tourist Visits (10^4 rooms)	17.71	14.17	1.04	52.89
K. brevis Cell Counts (10^7 cell counts/L)	0.31	1.68	0.00	16.22

* Includes ED visits by county residents and tourists aged 55 and older.

Table 3
Exposure–response models testing for relationships between measures of Florida red tides and Emergency Department (ED) visits for headache (ICD-9 784.0).

	ED/Headache	
Variable	Coefficient	*t* value
Intercept	3.27**	2.06
K. brevis Cell Counts	0.20**	2.37
Resident Population	0.78***	2.62
Tourism	−0.04	−0.62
January	0.40	0.62
February	−0.30	−0.42
March	1.30	1.55
April	−0.52	−0.74
May	0.37	0.56
June	−0.53	−0.80
July	−1.18*	−1.78
August	−1.31**	−2.02
September	−1.39**	−2.13
October	−0.96	−1.48
November	0.13	0.22
2005	−1.84***	−3.49
2006	−1.95***	−3.93
2007	−1.88***	−3.98
2008	−1.09**	−2.36
n	360	
R^2	0.18	

The results of time-series, cross-section regression model, estimated using equation (1) from Section 2.4. The table contains the results of a model run with patients aged ≥55 years in the following Florida counties: Hillsborough, Pinellas, Manatee, Sarasota, Charlotte, and Lee. Response variable: ED = Emergency Department visits for headache. Exposure variables: *K. brevis* Cell Counts = *Karenia brevis* cell counts in opportunistic water samples taken within 15 km of the coast of each county. Tourism is a measure of the occupation of hotel and motel rooms in each county. The baseline for the (0,1) dummy variables is December 2009. The symbols *, **, *** denote significance at $p \leq 0.10$, $p \leq 0.05$ and $p \leq 0.01$, respectively.

(≥55 years) cohort. Nearly 20% of the proportion of the total variation in emergency department visits for headache has been explained by the model, suggesting that other unexplained factors may be important contributors to this type of illness. The model found a significant positive effect of *K. brevis* blooms, leading to an increase in emergency department visits for a primary diagnosis of headache (Fig. 3, Supp. Fig. 3).

The coefficient on *K. brevis* blooms implies that a one unit increase (1 unit = 10^7 cell counts/L) would lead to 0.20 (± 0.08; $p = 0.019$) additional emergency department visits per month for headache in older individuals (≥55 years) in a county. There are minor, but calculable, illness costs associated with these increases in emergency department visits as explained further in the Discussion Section. The

Fig. 3. Annual maps of headache frequency as a correlate of *K. brevis* blooms (2005-09).
Distributions and cell densities of Florida red tide (*K. brevis*) blooms along the southwest Florida coast during the study period. Onshore shapes depict the incidence of headache (ICD-9 784.0) for persons ≥55 years in ZIP codes proximate to the coast. Rate calculations are stratified by age using population estimates at the ZIP code level (BoC, 2010). A monthly time-lapse video from January 2005-December 2009 is available in the Supplement (Supp. Fig. 3).

county population variable was also positively related to emergency department visits, revealing 0.78 (±0.30; $p << 0.01$) additional emergency department visits per month for headache—of all types—- with an increase of 100,000 residents in a county. The room occupancy rate was negatively related to emergency department visits for headache, but not statistically significant. Because this latter result appears to be counter-intuitive, a potential explanation is offered in the Discussion below.

To help interpret the categorical variables representing month and year, the model took a baseline of December 2009; the estimated coefficients on the categorical variables must be added to the estimated coefficient on the intercept of the model to assess their effects. The model revealed a seasonal fluctuation within a year; in any year, the fewest number of emergency department visits occurred during July-September and the highest occurred during November-January. Emergency department visits for headache were the lowest in 2006 and 2007 and the highest in 2009, when compared to other years in the study period.

4. Discussion

This study's results indicate a possible relationship between Florida red tide (blooms of the harmful alga, *K. brevis*) and emergency department visits for the specific neurological diagnosis of headache in older coastal residents. Using a similar analytical approach that did not examine neurological health outcomes, Hoagland et al. (2014) found an increased risk of respiratory and gastrointestinal diagnoses in the same Florida population segment (≥55 years) in coastal counties during active *K. brevis* blooms. Neurological illnesses have been theorized to result from human exposures to brevetoxins, but few studies have been undertaken to attempt to establish such a link. Fleming et al. (2005b, 2007; Kirkpatrick et al., 2011) observed a near-significant association (13/97; $p = 0.06$) between headache symptoms and a *K. brevis* bloom reported by asthmatic participants age 12–69 surveyed before and after a 1-hour beach walk during an active Florida red tide bloom, although this observation was not the main purpose of the study. Backer et al. (2005) observed a significant increase (23.5%; $p = 0.05$) in headache in lifeguards of age 19-51 working on Florida coastal beaches exposed to higher levels of red tide over a work day. In both studies, environmental testing for both aerosolized brevetoxins and *K. brevis* cells was carried out, and neither group reported increased incidence of headache in the absence of a Florida red tide.

Given the comparatively low frequency of emergency department visits due to headaches during Florida red tide, it is possible that this study underestimated the real risks of neurological illness, especially due to the numerous factors that disincentivize individuals from seeking medical care for what is arguably a common medical occurrence. Few people suffer severely enough to seek out medical care in an emergency context, therefore many more who may be suffering from headaches and migraines may decide to remain at work or at home. As noted earlier, presenteeism while suffering from an illness, such as a headache, results in decreased employee productivity and, in turn, a loss of economic benefits for employers. Presenteeism often can result from different external and internal factors that influence an employee to forego using a sick day (e.g., lack of health insurance, high deductible insurance plans, personal costs, including the opportunity costs of time, loss of income, or low severity of symptoms) (Aronsson et al., 2000). These indirect costs of brevotoxin-induced headaches should not be ignored. Further, the costs associated with affected individuals self-medicating with over-the-counter medications should be recognized.

The finding that changes in hotel and motel room occupancy were not correlated with emergency department visits for headache seems counter-intuitive. It is plausible that room occupancy data corresponded mainly to younger individuals visiting coastal counties for short periods of time. Consequently, these tourists are either exposed less often to aerosolized brevetoxin—and perhaps more likely to go inland during active Florida red tide blooms—or, alternatively, are less susceptible to brevetoxin when exposed. While it is important to control for variability in tourist visitation as a component of the larger exposed population, the absence of data on condominium and time-share occupancies may limit the ultimate relevance of room occupancy as a suitable measure of tourism. Given the overwhelming importance of tourism to the southwest Florida coastal economy, this aspect of the model deserves further research.

Although the incidence of headaches resulting from Florida red tide that are severe enough to warrant an emergency department visit appears to be fairly small, the model revealed a significant link between this incidence and the density of *K. brevis* blooms in the near coastal waters of a county. Using the baseline of December 2009 as a reference, emergency department visits for additional headaches due to Florida red tide in the coastal communities of a county characterized by the mean population size and mean hotel and motel room occupancies would range from one additional headache for a maximum count in a month of 1.0×10^7 cell counts/L to three additional headaches for a maximum count in a month of 16.2×10^7 cell counts/L. Assuming a marginal cost of a semi-urgent emergency department visit of $114 (Williams, 1996) and an average of four days of lost productivity at $120/day (*cf.* Hoagland et al., 2014; Stovner and Andrée, 2008), economic effects could range roughly between $500 to $900 in a county in a month. If such cell counts were to take place over a month off the coast of each of the six counties on an annual basis extending into the future, this suggests capitalized costs of illness (using a discount rate of 2%) ranging from $0.2–0.3 million for all coastal communities in the region.

The principal diagnosis for emergency department visits for headache was found specifically for persons aged 55 and older. Prior research (Hoagland et al., 2014) also identified persons aged 55 and older as at increased risk for respiratory and gastrointestinal emergency department and hospital visits during active Florida red tides. Some factors that could influence susceptibility in this age group include ineffectiveness of headache medication due to potential adverse effects, unidentified neurologic injury or cognitive decline, decreased lung function (Hershey and Bednarczyk, 2013), and possibly less ability or interest in leaving coastal areas exposed to the Florida red tide blooms. Further, individuals of age 65 and older (a majority of the group ≥ 55 years examined in this study) have access to health insurance through Medicare and may be retired from work, and therefore have no fear of loss of income when visiting an emergency department. These factors make an emergency department visit more likely in this older age group, but at the same time mitigating the costs of lost productivity.

In the present study, exposure was ecological, i.e. assumed due to geographic proximity and temporal concurrence at the county residence level; it did not rely upon observations of actual brevetoxin exposure or the pathway linking brevetoxins to any individual patient. Other limitations of this research include the difficulty confirming NSP and aerosolized brevetoxin effects because reliable human biomarkers for these toxins do not yet exist. Without confirmatory testing of shellfish (for NSP) or aerosol (for other illnesses) brevetoxin exposures, these diagnoses rely heavily upon patient self-reported symptoms and exposure histories, especially with neurological illnesses such as headache (Fleming et al., 2011; Friedman et al., 2017). Further, the possibility must be considered that headaches experienced by these patients could have been secondary to dehydration, respiratory symptomatology, or other non-neurologic causes, even when headache was the primary diagnosis.

The use of a primary diagnosis of headache for emergency department visits as the sole health outcome means that for any given individual, other factors could lead to such a diagnosis, including the possibility of over-diagnosis by healthcare providers trying to obtain higher reimbursements. During this time in Florida, a pilot program was implemented to discourage over-diagnosis by healthcare institutions. Therefore, when this program was operational, a principal diagnosis of headache seems more likely to have been an actual diagnosis.

Work by Kirkpatrick et al. (2010) has demonstrated that aerosolized brevetoxins can be transported by onshore wind up to 6.4 km inland from the coastal water source. In order to reduce the risk of exposure to brevetoxins, educational material should expand upon the current public health message, which recommends just avoidance of the immediate beach area, to reflect that brevetoxin aerosols may be present up to 6.4 km inland from the coast during active coastal Florida red tide blooms. These educational materials aim to reduce brevetoxin exposure among coastal residents and business patrons (Nierenberg et al., 2010, 2011).

In addition to educational materials on proper avoidance during active red tides and other forms of exposure risk reduction, healthcare providers should be aware of the increased risks that elderly patients or respiratory-compromised patients, such as asthmatics, face during active red tide blooms (Milian et al., 2007). Educating healthcare providers in potentially affected counties on the possible range of symptoms caused by aerosolized brevetoxins would expedite the rendering of an accurate diagnosis and increase treatment efficiency. Importantly, there is a clear need to recognize the potential for the miscommunication of risks, thereby potentially discouraging visitors from returning to coastal areas, leading to adverse impacts on coastal Florida tourism revenues and property values as well as the decrease of potential wellbeing gained through exposure to blue environments (White et al., 2016). In particular, the content of educational materials needs to be conveyed soberly and clearly, so that the exaggeration or misinterpretation of risks is minimized.

5. Conclusions

This study focused on the geographic and temporal associations between Florida red tide blooms and a range of neurologic principal diagnoses for emergency department visits. The southwest coast of Florida is an important location for older retirees and snowbirds, and both groups make up a significant portion of the combined resident and visitor populations. As a result, an observed increased risk in persons aged 55 and over for headache, as well as for respiratory and gastrointestinal diseases, is an important finding. Further, even though this study did not uncover an increased risk for headache in younger persons, as described above, prior research suggests that this risk may exist but that, for various reasons, individuals from these groups might not have sought emergency treatment. Headache is well-known as the cause for significant occurrences of morbidity and loss of productivity in working-age individuals.

Easily available, sensitive, and specific human biomarkers of brevetoxins are needed to further this research in the future; and healthcare providers should be instructed to consider brevetoxin exposures and resultant illnesses as possible diagnoses, particularly during active Florida red tide blooms. More work needs to be done to implement preventive measures designed to reduce and limit the exposure—particularly of older populations—during Florida red tide blooms.

Declaration of Interests

The authors declare no competing financial interests.

Author Contributions

R.E.D. and S.G.U. conceived the project. S.G.U., L.E.F., and P.H. supervised the project. R.E.D., D.J., A.B., A.R., and P.H. analyzed and interpreted data. R.E.D., M.A.F., B.K., G.K., S.G.U., L.E.F., and P.H. wrote the manuscript.

Acknowledgments

For help with compiling data, the authors thank Adrienne Henderson and Gloria Barker of the Florida Agency for Health Care Administration, Steve Hood of Smith Travel Research, Inc., Chris Knight of the Florida Department of Agriculture and Consumer Services, Benjamin A. Barad and Sy Redding at the University of California, San Francisco, and David Andres Ayala Usma at the Universidad de los Andes - Colombia. For help with ArcGIS, the authors thank Chidera Anugwom (University of Miami), Evan W. Knopf (Fehr & Peers), and Brooke Wikgren (New England Aquarium). The authors benefitted from discussions with Bruce Garrison, Gary Hitchcock, Damian Klambauer, Kate Kohler, Rebecca Lazensky, Zongchao (Cathy) Li, Vince Lovko, Katrin Rudge, Richard P. Stumpf, and Sharon Watkins. The use of Florida Agency for Health Care Administration data on human health outcomes was determined to meet IRB exempt criteria by the Human Subjects Research Office at the University of Miami.[SS]

Funding

This research was sponsored by the National Science Foundation (NSF) under NSF Grant No. CNH 1009106. P.H. and D.J. acknowledge complementary support under NSF Grant No. PFI/BIC 1534054. R.E.D. acknowledges support under NSF Grant No. 1650113. L.E.F. acknowledges support from the UK Natural Environment Research Council (NERC); and the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Environmental Change and Health at the London School of Hygiene and Tropical Medicine in partnership with Public Health England, and in collaboration with the University of Exeter, University College London, and the Met Office. The funders had no role in study design, data collection and interpretation, or decision to submit the work for publication. The views expressed are those of the author(s) and not necessarily those of the National Science Foundation, the English National Health Service, the National Institute for Health Research, the Florida Department of Health, or Public Health England.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.hal.2018.07.002.

References

Adams, C.S., Larkin, S.L., Mulkey, D., Hodges, A., Ballayram, A., 2002. Measuring the economic consequences and public awareness of red tide events in Florida. Harmful Algal Task Force. Florida Marine Research Institute, St. Petersburg, FL 145 pp.

Adams, C.M., Larkin, S.L., Hoagland, P., Sancewich, B., 2018. Assessing the economic consequences of harmful algal blooms: a summary of existing literature, research methods, data, and information gaps. In: Shumway, S.E. (Ed.), Harmful Algal Blooms: A Compendium Desk Reference. John Wiley & Sons, Inc, New York, pp. 337–354.

Arena, P., Levin, B., Fleming, L.E., Friedman, M.A., Blythe, D.G., 2004. A pilot study of the cognitive and psychological correlates of chronic ciguatera poisoning. Harmful Algae 3, 51–60.

Aronsson, G., Gustafsson, K., Dallner, M., 2000. Sick but yet at work. An empirical study of sickness presenteeism. Journal of Epidemiology and Community Health 54, 502–509.

Backer, L.C., Kirkpatrick, B., Fleming, L.E., Cheng, Y.S., Pierce, R., Bean, J.A., Clark, R., Johnson, D., Wanner, A., Tamer, R., Baden, D.G., 2005. Occupational exposure to aerosolized brevetoxins during Florida red tide events: impacts on a healthy worker population. Environmental Health Perspectives 113, 644–649.

Bean, J.A., Fleming, L.E., Kirkpatrick, B., Backer, L.C., Nierenberg, K., Reich, A., Cheng, Y.S., Wanner, A., Benson, J., Naar, J., Pierce, R., Abraham, W.M., Kirkpatrick, G., Hollenbeck, J., Zaias, J., Mendes, E., Baden, D.G., 2011. Florida red tide toxins (brevetoxins) and longitudinal respiratory effects in asthmatics. Harmful Algae 10, 744–748.

Benson, J.M., Gomez, A.P., Statom, G.L., Tibbetts, B.M., Fleming, L.E., Backer, L.C., Reich, A., Baden, D.G., 2006. Placental transport of brevetoxin-3 in CD-1 mice. Toxicon 48, 1018–1026.

Bureau of Labor Statistics (BLS), 2017. Consumer price index. [last accessed on February 22, 2018 at. U.S. Department of Labor, Washington]. http://www.bls.gov/cpi/.

Bureau of the Census (BoC), 2010. Age Groups and Sex: 2010. [last accessed on June 30, 2018 at. U.S. Department of Commerce, Washington]. http://www.census.gov/.

Bureau of the Census (BoC), 2013. Annual and decadal estimates of the resident population for counties of. [last accessed on September 30, 2013 at. U.S. Department of Commerce, Florida. Washington]. http://www.census.gov/.

Cheng, Y.S., Zhou, Y., Irvin, C.M., Pierce, R.H., Naar, J., Backer, L.C., Fleming, L.E., Kirkpatrick, B., Baden, D.G., 2005. Characterization of marine aerosol for assessment of human exposure to brevetoxins. Environmental Health Perspectives 113, 638–643.

Elston Lafata, J., Moon, C., Leotta, C., Kolodner, K., Poisson, L., Lipton, R.B., 2004. The Medical Care Utilization and Costs Associated with Migraine Headache. Journal of General Internal Medicine 19, 1005–1012.

Fish and Wildlife Research Institute (FWRI), 2013. HAB monitoring database. [last accessed on October 14, 2013 at. Florida Fish and Wildlife Conservation Commission, Tallahassee]. http://myfwc.com/research/redtide/monitoring/database/.

Fleming, L.E., Backer, L.C., Rowan, A., 2002. The Epidemiology of Human Illnesses Associated with Harmful Algal Blooms. In: In: Baden, D.G., Adams, D. (Eds.), Neurotoxicology handbook, vol. 1. Humana Press Inc, Totowa, pp. 363–381.

Fleming, L.E., Backer, L.C., Baden, D.G., 2005a. Overview of aerosolized Florida red tide toxins, exposures and effects. Environmental Health Perspectives 113, 618–620.

Fleming, L.E., Kirkpatrick, B., Backer, L.C., Bean, J.A., Wanner, A., Dalpra, D., Tamer, R., Zaias, J., Cheng, Y.S., Pierce, R., Naar, J., Abraham, W., Clark, R., Zhou, Y., Henry, M.S., Johnson, D., Van de Bogart, G., Bossar, G.D., Harrington, M., Baden, D.G., 2005b. Initial evaluation of the effects of aerosolized Florida red tide toxins (brevetoxins) in persons with asthma. Environmental Health Perspectives 113, 650–657.

Fleming, L.E., Kirkpatrick, B., Backer, L.C., Bean, J.A., Wanner, A., Reich, A., Zaias, J., Cheng, Y.S., Pierce, R., Naar, J., Abraham, W.M., Baden, D.G., 2007. Aerosolized red tide toxins (brevetoxins) and asthma. Chest 131, 187–194.

Fleming, L.E., Bean, J.A., Kirkpatrick, B., Cheng, Y.S., Pierce, R., Naar, J., Nierenberg, K., Backer, L.C., Wanner, A., Reich, A., Zhou, Y., Watkins, S., Henry, M., Zaias, J., Abraham, W.M., Benson, J., Cassedy, A., Hollenbeck, J., Kirkpatrick, G., Clarke, T., Baden, D.G., 2009. Exposure and effect assessment of aerosolized red tide toxins (Brevetoxins) and asthma. Environmental Health Perspectives 117, 1095–1100.

Fleming, L.E., Kirkpatrick, B., Backer, L.C., Walsh, C.J., Nierenberg, K., Clark, J., Reich, A., Hollenbeck, J., Benson, J., Cheng, Y.S., Naar, J., Pierce, R., Bourdelais, A.J., Abraham, W.M., Kirkpatrick, G., Zaias, J., Wanner, A., Mendes, E., Shalat, S., Hoagland, P., Stephan, W., Bean, J., Watkins, S., Clarke, T., Byrne, M., Baden, D.G., 2011. Review of Florida red tide and human health effects. Harmful Algae 20, 224–233.

Friedman, M.A., Arena, P., Levin, B., Fleming, L., Fernandez, M., Weisman, R., Bernstein, J., Schrank, K., Blythe, D., Backer, L., Reich, A., 2007. Neuropsychological study of ciguatera fish poisoning: A longitudinal case-control study. Archives of Clinical Neuropsychology 22, 545–553.

Friedman, M.A., Levin, B.E., 2005. Neurobehavioral effects of harmful algal bloom (HAB) toxins: A critical review. Journal of the International Neuropsychological Society 11, 331–338.

Friedman, M.A., Fleming, L.E., Fernandez, M., Bienfang, P., Schrank, K., Dickey, R., Bottein, M.Y., Backer, L.C., Ayyar, R., Weisman, R., Watkins, S., Granade, R., Reich, A., 2008. Ciguatera fish poisoning: treatment, prevention and management. Marine Drugs (Spcl. Iss. Mar. Tox.) 6, 456–479.

Friedman, M.A., Fernandez, M., Backer, L.C., Dickey, R.W., Bernstein, J., Schrank, K., Kibler, S., Stephan, W., Gribble, M.O., Bienfang, P., Bowen, R.E., Degrasse, S., Flores Quintana, H.A., Loeffler, C.R., Weisman, R., Blythe, D., Berdalet, E., Ayyar, R., Clarkson-Townsend, D., Swajian, K., Benner, R., Brewer, T., Fleming, L.E., 2017. An updated review of ciguatera fish poisoning: clinical, epidemiological, environmental, and public health management. Marine Drugs 15, 72.

Habas, E.J., Gilbert, C., 1975. A preliminary investigation of the economic effects of the HAB of 1973–1974 on the west coast of Florida. In: LoCicero, V.R. (Ed.), Proceedings of the first international conference on toxic dinoflagellate blooms. The Massachusetts Science and Technology Foundation, Boston, pp. 499–505.

Hershey, L.A., Bednarczyk, E.M., 2013. Treatment of headache in the elderly. Current Treatment Options in Neurology 15, 56–62.

Hoagland, P., Anderson, D.M., Kaoru, Y., White, A.W., 2002. The economic effects of harmful algal blooms in the United States: estimates, assessment issues, and information needs. Estuaries 25, 819–837.
Hoagland, P., Jin, D., Polansky, L.Y., Kirkpatrick, B., Kirkpatrick, G., Fleming, L.E., Reich, A., Watkins, S.M., Ullmann, S.G., Backer, L.C., 2009. The costs of respiratory illnesses arising from Florida Gulf Coast *Karenia brevis* blooms. Environmental Health Perspectives 117, 1239–1243.
Hoagland, P., Jin, D., Beet, A., Kirkpatrick, B., Reich, A., Ullmann, S., Fleming, L.E., Kirkpatrick, G., 2014. The human health effects of Florida red tide blooms: an expanded analysis. Environment International 68, 144–153.
Kirkpatrick, B., Fleming, L.E., Backer, L.C., Bean, J.A., Tamer, R., Kirkpatrick, G., Kane, T., Wanner, A., Dalpra, D., Reich, A., Baden, D.G., 2006. Environmental exposures to Florida red tides: effects on emergency room respiratory diagnoses admissions. Harmful Algae 5, 526–533.
Kirkpatrick, B., Bean, J.A., Fleming, L.E., Kirkpatrick, G., Grief, L., Nierenberg, K., Reich, A., Watkins, S., Naar, J., 2009. Gastrointestinal emergency room admissions and Florida red tide blooms. Harmful Algae 9, 82–86.
Kirkpatrick, B., Pierce, R., Cheng, Y.S., Henry, M.S., Blum, P., Osborn, S., Nierenberg, K., Pederson, B.A., Fleming, L.E., Reich, A., Naar, J., Kirkpatrick, G., Backer, L.C., Baden, D.G., 2010. Inland transport of aerosolized Florida red tide toxins. Harmful Algae 9, 186–189.
Kirkpatrick, B., Fleming, L.E., Bean, J.A., Nierenberg, K., Backer, L.C., Cheng, Y.S., Pierce, R., Reich, A., Naar, J., Wanner, A., Abraham, W.M., Zhou, Y., Hollenbeck, J., Baden, D.G., 2011. Aerosolized red tide toxins (brevetoxins) and asthma: continued health effects after 1-hour beach exposure. Harmful Algae 10, 138–143.
Larkin, S.L., Adams, C.M., 2007. Red tides and coastal businesses: measuring economic consequences in Florida. Society and Natural Resources 20, 849–859.
McFarren, E.F., Tanabe, H., Silva, F.J., Wilson, W.B., Campbell, J.E., Lewis, H.K., 1965. The occurrence of ciguatera-like poison in oysters, clams and Gymnodinium breve cultures. Toxicon 3, 111–123.
Milian, A., Nierenberg, K., Fleming, L.E., Bean, J.A., Wanner, A., Reich, A., Backer, L.C., Jayroe, D., Kirkpatrick, B., 2007. Reported respiratory symptom intensity in asthmatics during exposure to aerosolized Florida red tide toxins. Journal of Asthma 44, 583–587.
Morgan, K.L., Larkin, S.L., Adams, C.M., 2009. Empirical analysis of media versus environmental impacts on park attendance. Tourism Management 32, 852–859.
Morgan, K.L., Larkin, S.L., Adams, C.M., 2010. Firm-level economic effects of HABS: a tool for business loss assessment. Harmful Algae 8, 212–218.
Nierenberg, K., Byrne, M., Fleming, L.E., Stephan, W., Reich, A., Backer, L.C., Tanga, E., Dalpra, D., Kirkpatrick, B., 2010. Florida red tide perception: residents versus tourists. Harmful Algae 9, 600–606.
Nierenberg, K., Hollenbeck, J., Fleming, L.E., Stephan, W., Reich, A., Backer, L.C., Currier, R., Kirkpatrick, B., 2011. Frontiers in outreach and education: the Florida red tide experience. Harmful Algae 10, 374–380.
Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H.-U., Jönsson, B., 2012. The economic cost of brain disorders in Europe. European Journal of Neurology 19, 155–162.
Pizzo, P.A., Clark, N.M., 2011. Preface. Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. National Academies Press, Washington, pp. ix–xiii.
QGIS Development Team, 2018. QGIS Geographic Information System. Open Source Geospatial Foundation Project. [last accessed on June 26, 2018 at.]. http://qgis.osgeo.org.
Reich, A., Lazensky, R., Faris, J., Fleming, L.E., Kirkpatrick, B., Watkins, S., Ullmann, S., Kohler, K., Hoagland, P., 2015. Assessing the impact of shellfish harvesting area closures on neurotoxic shellfish poisoning (NSP) incidence during red tide (*Karenia brevis*) blooms. Harmful Algae 43, 13–19.
Smith Travel Research, Inc. (STR), 2013. Customized data on Florida county hotel and motel occupancy and rental rates. STR SHARE Center, Hendersonville, TN.
Stewart, W.F., Ricci, J.A., Chee, E., Morganstein, D., Lipton, R., 2003. Lost productive time and cost due to common pain conditions in the US workforce. Journal of the American Medical Association 290, 2443–2454.
Stovner, L.J., Andrée, C., 2008. Impact of headache in Europe: a review for the Eurolight Project. Journal of Headache and Pain 9, 139–146.
University of Florida GeoPlan Center, 2015. Florida County Boundaries - September 2015. [last accessed on June 26, 2018 at.]. http://www.fgdl.org.
University of Florida GeoPlan Center, 2012. ZIP Code Areas (Five-Digit) in Florida - 2012. [last accessed on June 26, 2018 at.]. http://www.fgdl.org.
Watkins, S.M., Reich, A., Fleming, L.E., Hammond, R., 2008. Neurotoxic shellfish poisoning. Marine Drugs (Spcl. Iss. Mar. Tox.) 6, 431–455.
White, M.P., Pahl, S., Wheeler, B.W., Fleming, L.E., Depledge, M.H., 2016. 'Blue Gym': What can blue space do for you and what can you do for blue space? Journal of the Marine Biological Association of the United Kingdom 96, 5–12.
Williams, R.M., 1996. The costs of visits to emergency departments. New England Journal of Medicine 334, 642–645.