Water recreation and illness severity

Stephanie DeFlorio-Barker, Timothy J. Wade, Mary Turyk and Samuel Dorevitch

ABSTRACT

The health endpoint of prior studies of water recreation has been the occurrence of gastrointestinal (GI) illness. This dichotomous measure fails to take into account the range of symptom severity among those with GI illness, and those who develop GI symptoms but who do not satisfy the definition of GI illness. Data from two US cohort studies were used to assess use of ordinal and semi-continuous measures of GI symptoms, such as duration of GI symptoms and responses to those symptoms such as medication use, interference with daily activities, and utilization of healthcare service. Zero-inflated negative binomial and logistic regression models were used to assess associations between severity and either the degree of water exposure or water quality. Among 37,404 water recreators without baseline GI symptoms, we observed individuals with relatively low severity satisfying the case definition of GI illness, while others with high severity not satisfying that definition. Severity metrics were associated with water exposure. The dichotomous GI illness outcome could be improved by considering symptom severity in future studies. Modeling ordinal and semi-continuous outcomes may improve our understanding of determinants of the burden of illness rather than simply the number of cases of illness attributable to environmental exposures.

Key words | fecal indicator bacteria, gastrointestinal illness, illness severity, water recreation

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INTRODUCTION

Over the past 60 years epidemiologic studies have evaluated risk due to water recreation on US surface waters by comparing rates of gastrointestinal (GI) illness occurrence among recreators as a function of water quality and water exposure (Stevenson 1953; Cabelli 1983; Dufour 1984; Wade *et al.* 2008). *Escherichia coli* (*E. coli*) and enterococci ('indicator bacteria') have been identified as predictors of the occurrence of GI illness among water recreators (Cabelli 1983; Dufour 1984). In those epidemiologic studies, GI illness was defined as the presence or absence of a set of symptoms, though the specific elements of that set varied among studies. Relationships between water quality and the risk of GI illness occurrence observed in many of these studies have been used to inform water quality criteria recommendations (US EPA 1986, 2012).

As a result of this binary classification system of illness, potentially important distinctions in disease severity are lost. A definition of GI illness used in recent epidemiology studies of recreational water exposure (Wade *et al.* 2006, 2008, 2010; Dorevitch *et al.* 2012) was diarrhea (three or more loose stools in 24 hours), or vomiting, or nausea with stomachache, or nausea that interferes with daily activities, or stomachache that interferes with daily activities. Consider three individuals, all of whom developed GI symptoms as a result of exposure to recreational waters. Case A experienced two loose stools over a 24-hour period, took over-the-counter (OTC) medication for her symptoms, and missed 1 day of work due to symptoms. Case B had three loose stools over a 24-hour period but did not require medical treatment, and did not miss work.

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Case C had several bouts of vomiting and loose stools per day for 3 days, became dehydrated and received intravenous fluids in an emergency department (ED). Even though cases A and B seem similar to one another, A would be considered to not have GI illness, while case B would. Furthermore, the substantial difference in symptom severity and resulting medical treatment between cases B and C would not be captured by the binary classification system.

Presently, no 'gold standard' definition exists for GI symptoms resulting from waterborne (or any other) exposures. Evaluating measures of symptom severity on an ordinal scale, rather than considering illness occurrence as a dichotomous definition, may lead to better understanding of risks, predictors, and consequences of recreational waterborne illness. We utilized data from two epidemiologic studies of water recreation to characterize the severity of symptoms among water recreators, highlight differences between a binary and an ordinal classification system, and evaluate the relationship between symptom severity and water quality or water exposure. Limited data support an association between a higher dose of infectious pathogens and greater symptom severity among human volunteers (Glynn *et al.* 1995). Thus, a range of fecal indicator concentrations in surface water might be associated with a continuum of symptom severity among water recreators.

METHODS

Study population

The National Epidemiological and Environmental Assessment of Recreational Water (NEEAR) study evaluated health risks (including GI, respiratory, ear, eye, or skin symptoms) of swimming and wading at marine and freshwater beaches impacted by human fecal pollution in Alabama, Indiana, Michigan, Mississippi, Ohio, and Rhode Island. During 2003–2007, beachgoers with and without beach water contact were recruited. Recruiting, survey administration, and corresponding water sampling methods have been described previously (Wade *et al.* 2008, 2010).

The Chicago Health Environmental Exposure and Recreation Study (CHEERS) evaluated health risks of incidental-contact water recreation (boating, canoeing, fishing, kayaking, and rowing). During 2007–2009, participants were recruited from 39 locations in the Chicago, Illinois area, including Lake Michigan, small inland lakes, and the Chicago River system, which, at the time of this study, was predominantly treated wastewater effluent (Rijal *et al.* 2011). An unexposed group, people engaged in outdoor recreation that did not involve water, was recruited as well. Study protocols, questionnaires and the general design were based on NEEAR. Survey and water quality assessment methods for CHEERS have been described previously (Dorevitch *et al.* 2012, 2015).

Illness outcome definitions

Some studies have found that the strongest association between GI illness and water recreation was observed within 0–3 days following recreational activity (Dorevitch *et al.* 2012; Arnold *et al.* 2013). In the current analysis, acute gastrointestinal illness (AGI), was defined as illness, meeting the aforementioned case definition used in previous studies (Wade *et al.* 2006, 2008, 2010; Dorevitch *et al.* 2012), within 0–3 days of recreation. Severity was assessed among those with AGI, as well as those who had incident symptoms within 0–3 days of water recreation but did not meet the AGI case definition.

CHEERS and NEEAR study protocols were not identical. In NEEAR, one adult member per household provided information during a single telephone interview 10–12 days following the recreation event about all participating family members (Wade *et al.* 2006, 2008, 2010). In CHEERS, participants provided follow-up information about themselves, except in the case of children <8 years old whose information was provided by parents (children of 8–17 years were allowed to answer on their own, but were assisted by parents). Participants were interviewed via telephone on approximately days 2, 5, and 21 following the recreation event (Dorevitch *et al.* 2012). In CHEERS, follow-up telephone interviews captured information about the number of loose stools per individual in a 24-hour period, however, in NEEAR, the number of loose stools was not ascertained, only whether that number was at least three. Therefore, among CHEERS participants, reports of less than three loose stools were excluded from the definition of GI symptoms (NEEAR definition) to improve comparability of information between the studies. Additionally, all symptoms reported (including those with less than three loose stools) (CHEERS definition) are also included in the analysis, to compare the two definitions (NEEAR versus CHEERS definition).

Severity metrics

Severity metrics, or scores, were based on information collected in NEEAR and CHEERS. Severity was assessed for all participants that developed GI symptoms within 0–3 days of water recreation, regardless of whether they met the case definition for AGI. Those that did not develop symptoms were assigned a severity score of zero. First, the duration of GI symptoms was assessed (Supplemental material, available with the online version of this paper). Since CHEERS had a longer follow-up, symptoms lasting longer than 10–12 days were truncated at 12 days, to make the results comparable to those of NEEAR. The metric 'symptom-days (SDs)' was created by summing the number of symptoms and the duration (in days) of each symptom. Two SDs metrics were developed: for only GI symptoms (diarrhea, vomiting, nausea, or stomachache), and for total symptoms (all GI, respiratory, ear, eye, or skin symptoms). It has been suggested that more attention should be placed on more severe symptoms, such as vomiting and diarrhea (Freedman *et al.* 2010). Therefore, in calculating SDs, we weighted the duration of vomiting and diarrhea by a factor of two; duration of nausea and stomachache were weighted by a factor of one. For example, a person can have a duration of GI symptoms equivalent to two, but have nausea for 2 days and vomiting for 1 day. Therefore, their GI SDs would be equivalent to four (2 days of nausea + (1 day of vomiting × 2)).

Severity was also assessed according to 'responses to symptoms'. We assumed that symptom severity influences the decision to take medication, to visit a healthcare provider (HCP) or to stay home from work or school (Stratmann 1999; Scallan *et al.* 2006). During telephone follow-up for both NEEAR and CHEERS, participants were asked if they stayed home from work or school, took OTC medication, took prescription medication, contacted a HCP, or were admitted to an ED or hospital. Previous analyses of foodborne illness have considered illnesses that result in contact with a HCP to be more severe than illnesses that require no contact (Hoffmann *et al.* 2012). Therefore, participants who took prescription medication, contacted a HCP, lost time from work/school or daily activities, or went to an ED or hospital had a major response to symptoms, while all others with symptoms were considered to have a minor or no response.

Severity metrics were evaluated using χ^2 and the Kruskal Wallis test, where appropriate, to determine if any significant differences in severity existed among those with AGI compared to those with symptoms only.

Recreational water exposure

Water exposure was evaluated by post-recreation interviews. NEEAR participants who were only wet below their waist were considered waders, while those wet above the waist were considered swimmers (Wade *et al.* 2008). The degree of water exposure among NEEAR water recreators was defined on an ordinal scale: (1) swimmers who swallowed water, (2) swimmers who did not swallow water, and (3) waders (reference group). For CHEERS water recreators, the three ordinal categories were: (1) those who swallowed water; (2) those who did not swallow water but got their face, torso, or hands wet; and (3) those who reported no water exposure (reference group). NEEAR participants who reported no water contact and CHEERS participants who did not participate in water recreation were excluded from all analyses, which focus on water quality and water exposure as a predictor of symptom severity, as they had no water exposure.

Exposure to increased levels of fecal contamination in recreational water was hypothesized to be related to symptom severity because it could increase the quantity of pathogens ingested by the recreators. Dose of pathogens has been demonstrated to be related to the occurrence of GI illness in an outbreak at an Oregon lake (Keene *et al.* 1994) and has been suggested to be directly related to severity of symptoms in outbreaks of salmonellosis (Taylor *et al.* 1984; Glynn & Bradley 1992; Mertens *et al.* 2013) and studies related to hepatitis E (Purcell & Emerson 2008).

Surface water was sampled during water recreation. Among NEEAR water recreators we assessed severity in relation to enterococci by both a culture-based method (US EPA Method 1600) and by quantitative polymerase chain reaction (qPCR) (comparable to US EPA Method 1611). The qPCR method measures enterococci DNA, regardless of whether bacteria are viable and culturable. Among CHEERS water recreators we assessed severity in relation to concentrations of viable and culturable enterococci (US EPA Method 1600) and F+ coliphage (US EPA Method 1602). Male-specific (F+) coliphages, viruses that infect *E. coli* with pili, are thought to have similar fate and transport as viral pathogens in surface water (Colford *et al.* 2007; Bosch 2010). Daily mean water quality measurements from both studies were utilized in this analysis. Due to differences in water quality in both studies, quartiles and dichotomization at the 75th percentiles were calculated separately.

Severity associated with water exposure and fecal indicator organisms

We considered the duration of GI symptoms and SDs to be count outcomes, and assessed the relationship between these severity metrics and water exposure and fecal indicators using zero-inflated negative binomial (ZINB) regression, since many participants did not develop symptoms and were considered to have no severity. Zero-inflated models utilize two separate processes for fitting models: a logistic process to evaluate zeros versus non-zeros (symptoms vs. no symptoms), and a negative binomial process to evaluate the non-zero values (extent of severity among those with symptoms) (Hilbe 2011). Exponentiating beta values from negative binomial regression of event occurrence data yields the incidence rate ratio. Because incidence rate ratio could be misconstrued as the ratio of incidence rates, rather than the ratio of symptom severity, we refer to this as the duration ratio or the SDs ratio, since it represents the duration or number of SDs compared to the reference group. Responses to symptoms (use of medication, missing work, etc.) were assessed as a binary outcome, using logistic regression. Variables that were identified in prior analyses of NEEAR and CHEERS as potential confounders of associations between water exposure and GI illness (Wade *et al.* 2006, 2008, 2010; Dorevitch *et al.* 2012) were considered in multivariate regression models between water exposure and symptom severity (Supplementary Figure S2, Supplementary Table S1, available with the online version of this paper). A change-in-estimate analysis, using a list of potential confounders, identified confounders that resulted in at least a 5% change in the final measure of association between water exposure and symptom severity, were retained in the final model (Lee 2014). Age and comorbidities were thought to potentially modify the association between water exposure and severity, because those at the extremes of age or with comorbid conditions have been found to develop more severe symptoms after exposure to enteric microorganisms (Szilagyi *et al.* 1985; Glynn & Bradley 1992; Karaoglu *et al.* 2004; Lund & O'Brien 2011; Rocourt 2014). Separate models with multiplicative interactive terms between each of these factors and water quality were evaluated. Stratum-specific measures of association were assessed for interaction p-values <0.20. All models using NEEAR data controlled for beach as a fixed effect, and household cluster was also accounted for in logistic models. No clustering was evident in CHEERS. All data were analyzed using SAS® 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Study population

The NEEAR data set consisted of 27,276 participants of whom 17,571 were water recreators, who engaged in telephone follow-up (Table 1). CHEERS had 11,297 participants of whom 7,710 were water recreators, who engaged in telephone follow-up (Table 2). In general water recreators tended to be younger compared to non-water recreators. In both studies, a greater fraction of water recreators who swallowed water developed GI symptoms within 0–3 days of recreation compared to those with less water exposure or to non-water recreators. Among CHEERS participants, those with GI symptoms were defined according to the data available in CHEERS and according to the data available in NEEAR (Table 1). When including those with less than three loose stools in a 24-hour period (CHEERS definition), there were more participants in CHEERS which could be considered to have GI symptoms.

Severity and illness incidence

In both studies, those with AGI were significantly more likely, based on χ^2 testing, to miss work or daily activities, take OTC medications, or contact a HCP due to their symptoms compared to those with GI symptoms but without AGI (Table 3, Figure 1). However, those meeting the case definition for AGI were not always more likely to report more severe symptoms. For example, among the 373 CHEERS participants with

Table 1 | Demographics and symptoms by water exposure, among NEEAR participants[a]

	Swimmers, swallow water ($n = 2,300$)	Swimmers, did not swallow water ($n = 10,475$)	Waders ($n = 4,268$)	Non-water recreators ($n = 9,363$)
Age (years)				
0–10	1,326 (59.4)	2,646 (25.9)	643 (15.3)	824 (8.9)
11–19	411 (18.4)	1,953 (19.1)	428 (10.2)	1,013 (11.0)
20–54	455 (20.4)	5,150 (50.5)	2,738 (65.3)	6,106 (66.2)
≥ 55	42 (1.9)	453 (4.4)	383 (9.1)	1,284 (13.9)
Sex				
Male	1,247 (54.2)	4,944 (47.3)	1,571 (36.8)	3,867 (41.3)
Female	1,052 (45.8)	5,506 (52.7)	2,694 (63.2)	5,492 (58.7)
Race				
White	1,683 (73.3)	8,238 (79.0)	3,579 (84.2)	7,428 (79.4)
Black	184 (8.0)	520 (5.0)	248 (5.8)	674 (7.2)
Hispanic	314 (13.7)	1,287 (12.3)	261 (6.1)	906 (9.7)
Other/multiple	114 (5.0)	385 (3.7)	165 (3.9)	341 (3.8)
AGI (0–3 days)[b]	119 (5.0)	432 (4.0)	122 (2.7)	226 (2.3)
Any GI symptoms (0–3 days)	146 (6.1)	524 (4.8)	145 (3.3)	299 (3.1)
Responses to symptoms, n (%)				
OTC	83 (56.9)	290 (55.6)	85 (58.6)	163 (54.2)
Prescription	24 (16.6)	50 (9.5)	18 (12.5)	40 (13.4)
Contact with HCP	32 (21.9)	76 (14.5)	25 (17.4)	58 (19.4)
ED/Hospitalization	4 (2.7)	7 (1.3)	4 (2.8)	7 (2.3)
Missed work/activities	54 (37.0)	205 (39.1)	57 (39.3)	113 (37.8)
Duration of GI symptoms, mean (median)	2.8 (2.0)	3.1 (2.0)	3.0 (2.0)	3.3 (2.0)
GI SDs[c], mean (median)	5.7 (4.0)	6.4 (4.0)	5.9 (4.0)	6.5 (4.0)
Total SDs[d], mean (median)	9.3 (6.0)	8.9 (6.0)	9.3 (6.0)	10.0 (6.0)

[a]Excludes those with baseline GI symptoms.
[b]Meet case definition for AGI.
[c]Summation of days of enteric illness (nausea, stomach ache, diarrhea, vomiting).
[d]Summation of total days of enteric (GI) and non-enteric illness (respiratory, ear, eye, skin).

GI symptoms but without AGI, 47% took OTC medications and 57% participants reported two or more GI SDs. Likewise, among 215 NEEAR participants who had GI symptoms but not AGI, 49% took OTC medications and 42% reported two or more GI SDs. Conversely, 27% of CHEERS participants and 28% of NEEAR participants who met the definition of AGI reported none of the following: OTC or prescription medication use, seeking help from a HCP, being admitted to the hospital or ED, or missing work or daily activities. Likewise, no significant difference in the proportion admitted to a hospital or ED, or who took prescription medications in either study, differed among those with AGI compared to those with GI symptoms, but without AGI.

Water quality

In NEEAR, daily geometric mean enterococci measured by culture ranged from 0.3 colony forming units (CFU)/100 mL to 1,042.1 CFU/100 mL, with the 75th percentile of 43.0 CFU/100 mL. Enterococci measured using qPCR ranged from 5.8 calibrator cell equivalents (CCE)/100 mL to 1,442.7 CCE/100 mL with a 75th percentile of

Table 2 | Demographics and symptoms by water exposure among CHEERS participants[a]

	Swallow water (n = 284)	Body wetness (n = 4,748)	No water contact (n = 2,498)	Non-water recreators (n = 3,468)
Age (years)				
0–10	4 (1.4)	211 (4.4)	256 (10.3)	200 (5.8)
11–19	29 (10.2)	586 (12.3)	344 (13.8)	244 (7.0)
20–54	221 (77.8)	3,336 (70.3)	1,439 (57.6)	2,347 (67.7)
≥ 55	30 (10.6)	615 (13.0)	459 (18.4)	675 (19.5)
Sex				
Male	165 (58.1)	2,671 (56.3)	1,287 (51.5)	1,703 (49.1)
Female	119 (41.9)	2,077 (43.7)	1,211 (48.5)	1,765 (50.9)
Race				
White	227 (79.9)	3,917 (82.6)	1,839 (73.7)	2,202 (63.6)
Black	8 (2.8)	129 (2.7)	270 (10.8)	553 (16.0)
Hispanic	16 (5.6)	257 (5.4)	164 (6.6)	321 (9.3)
Other/multiple	33 (11.6)	441 (9.3)	222 (8.9)	385 (11.1)
AGI (0–3 days)[b]	18 (5.9)	203 (4.2)	94 (3.6)	116 (3.2)
Any GI symptoms (0–3 days) (CHEERS definition)[c]	45 (14.9)	480 (9.9)	212 (8.3)	291 (8.1)
Any GI symptoms (0–3 days) (NEEAR definition)[d]	38 (12.6)	381 (7.8)	162 (6.4)	223 (6.2)
Responses to symptoms, n (%)				
OTC	21 (55.3)	190 (49.9)	86 (53.1)	125 (56.1)
Prescription	0 (0.0)	17 (4.5)	7 (4.3)	25 (11.2)
Contact with HCP	4 (10.5)	34 (8.9)	16 (10.0)	43 (19.3)
ED/Hospitalization	1 (2.6)	2 (0.5)	0 (0.0)	8 (3.6)
Missed work/activities	15 (39.4)	108 (28.4)	56 (34.6)	82 (36.7)
Duration of GI symptoms, mean (median)	3.0 (2.0)	2.5 (2.0)	2.5 (2.0)	2.7 (2.0)
GI SDs[e], mean (median)	5.0 (3.0)	4.4 (2.0)	4.6 (2.0)	4.3 (2.5)
Total SDs[f], mean (median)	5.8 (3.0)	5.3 (3.0)	5.2 (3.0)	5.4 (3.0)

[a]Excludes those with baseline GI symptoms.
[b]Meet case definition for AGI.
[c]Have GI symptoms, but may or may not meet the case definition of illness; includes CHEERS participants who only reported ≤2 loose stools.
[d]Have GI symptoms, but may or may not meet the case definition of illness; excludes CHEERS participants who only reported ≤2 loose stools, to be more comparable to the NEEAR study.
[e]Summation of days of enteric illness (nausea, stomach ache, diarrhea, vomiting).
[f]Summation of total days of enteric (GI) and non-enteric illness (respiratory, ear, eye, skin).

169.2 CCE/100 mL. In CHEERS, water quality varied greatly according to the type of surface water being assessed. The Chicago River system was one of the locations for participant enrollment and water quality monitoring. At the time of the study, the majority of the flow through the Chicago River system was secondary treated but non-disinfected wastewater effluent (Rijal *et al.* 2011), resulting in much higher concentrations of both F+ coliphage and enterococci by culture compared to waterbodies such as Lake Michigan and inland lakes (Dorevitch *et al.* 2015). Water quality measurements were dichotomized at the 75th percentile for all combined water locations. The concentration of F+ coliphage ranged from 1.0 plaque forming units (PFU)/100 mL to 834.0 PFU/100 mL, with the 75th percentile at 16.1 PFU/100 mL. The concentration of enterococci by culture in CHEERS ranged from 0.1 to

Table 3 | Distribution of severity metrics for all participants who developed GI symptoms within 0–3 days following recreation

	AGI				GI symptoms[a]					GI symptoms (CHEERS definition)[b]				
	n	Range	Mean	Median	n	Range	Mean	Median	Z score[c], *p*-value	n	Range	Mean	Median	Z score[c], *p*-value
CHEERS														
Duration of GI symptoms (days)	352	1–13	2.9	2.0	314	1–13	2.2	1.5	−5.1, <0.01	522	1–13	2.1	1.0	–7.1, <0.01
GI SDs[d]	352	1–46	6.4	4.0	314	1–18	2.2	2.0	−15.2, <0.01	522	1–38	3.6	2.0	–10.9, <0.01
Total SDs[e]	370	1–56	7.3	4.0	324	1–32	3.1	2.0	−13.1, <0.01	535	1–40	4.3	2.0	–9.7, <0.01
NEEAR														
Duration of GI symptoms (days)	900	1–13	3.2	2.0	213	1–11	2.6	1.0	−5.4, <0.01	–	–	–	–	–
GI SDs[d]	900	1–64	7.2	4.0	213	1–11	2.6	1.0	−14.7, <0.01	–	–	–	–	–
Total SDs[e]	900	1–163	10.4	6.0	213	1–38	4.8	2.0	−11.0, <0.01	–	–	–	–	–

[a]GI symptoms, but not AGI; excludes CHEERS participants only reporting ≤2 loose stools.
[b]GI symptoms, but not AGI; includes CHEERS participants only reporting ≤2 loose stools.
[c]Non-parametric significance test comparing severity metrics for those with GI illness to those with GI symptoms only.
[d]Includes GI and non-GI symptoms.
[e]Summation of days of enteric illness (nausea, stomach ache, diarrhea, vomiting).
[f]Summation of total days of enteric (GI) and non-enteric illness (respiratory, ear, eye, skin).

18,318.1 CFU/100 mL, with the 75th percentile at approximately 463.8 CFU/100 mL.

Severity associated with water exposure and fecal indicator organisms

No statistically significant duration ratios and SDs ratios were observed among NEEAR water recreators swallowing water and swimming compared to waders for all semi-continuous severity outcomes using the ZINB model (Table 4). However, enterococci by qPCR appeared to be an important predictor of duration of GI symptoms (duration ratio = 1.54 (95% CI: 1.04, 2.28)) and GI SDs (SDs ratio = 1.42 (95% CI: 1.10, 1.84)) in the ZINB models (Table 4). Results of logistic regression showed that major responses to symptoms (hospitalization, ED visit, HCP visit or phone call, prescription medication use, or missing work or missing daily activities, vs. only taking OTC medications or having no response to symptoms) were more likely among those with greater water exposure. Greater water exposure among NEEAR participants (swimming with swallowing water vs. wading) was associated with increased odds of reporting major responses to symptoms (OR = 1.57 (95% CI: 1.27, 1.95)). However, microbial measures of water quality concentrations were not associated with a major response to symptoms among NEEAR participants. No differences were observed for any outcome when assessing water quality in quartiles, rather than a dichotomous outcome among NEEAR participants (Supplementary Table S2, available with the online version of this paper).

Similar to NEEAR, no statistically significant associations were observed among CHEERS water recreators swallowing water and having body wetness compared to water recreators with no water contact for all semi-continuous severity outcomes using the ZINB model (Table 5). In addition, semi-continuous measures of severity were not associated with exposures to fecal indicator microbes, when dichotomized at the 75th percentile or when assessed as quartiles (Supplementary Table S3, available with the online version of this paper). However, greater water exposure among CHEERS participants (swallowing water or body wetness vs. water recreators with no water contact) was associated with an increased odds of reporting major responses to symptoms (OR = 1.50 (95% CI: 0.98, 2.30) and OR = 1.29 (95% CI: 1.06, 1.57), respectively). However, when dichotomized at the 75th percentile, concentrations of fecal microbes were not

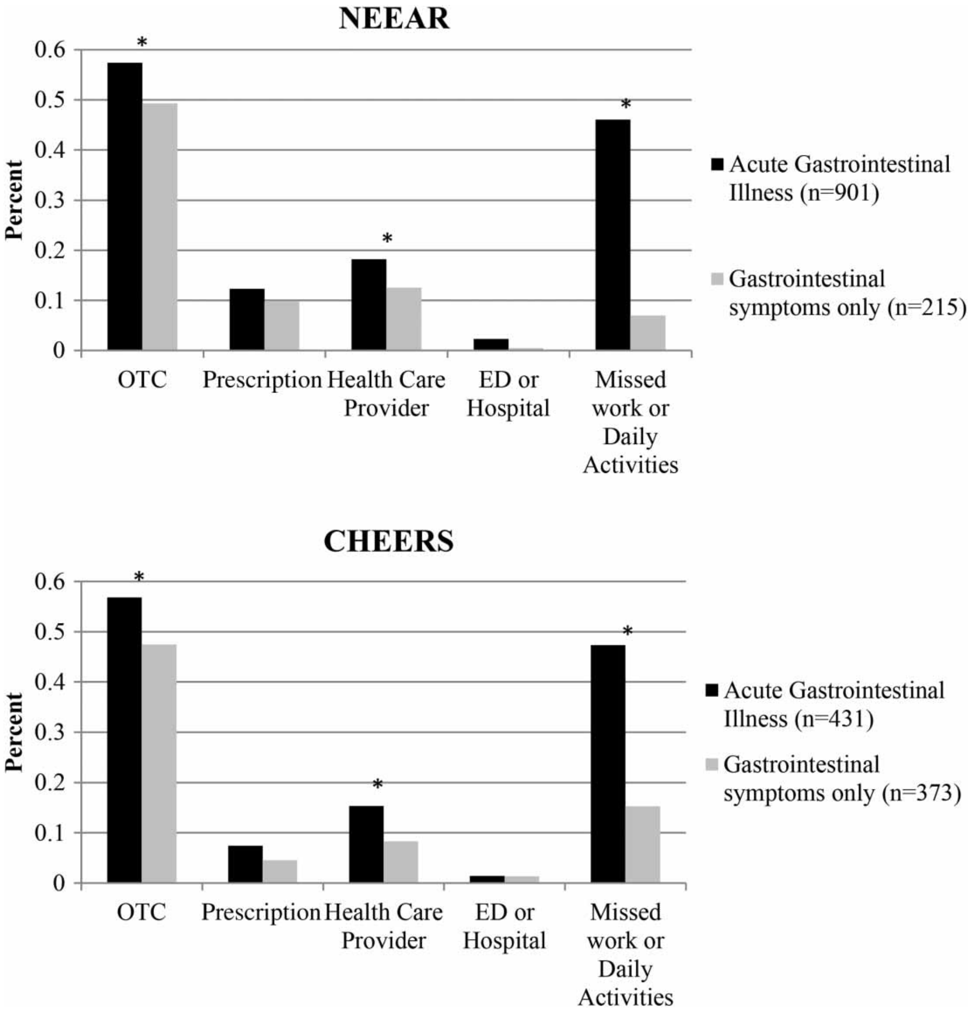

Figure 1 | Proportion of those who respond to symptoms. Those with GI symptoms only, do not meet the case definition for AGI. An (*) indicates χ^2 *p*-value $\leq$0.05.

associated with major responses to symptoms among CHEERS participants. When assessing the relationship between quartiles of F+ coliphage and major responses to illness, we observed a significant association between quartile 2 compared to quartile 1. However, this association was not observed in comparisons of response to illness among participants who recreated in water with F+ coliphage concentrations above the median (Supplementary Table S3).

Model details can be found in Supplementary Tables S4 and S5 (available with the online version of this paper). Additional ZINB models using unexposed non-water recreators as a reference group can be found in Supplementary Tables S6 and S7 (available with the online version of this paper). Overall, there were no major impacts on the results when non-water recreators were considered as the reference group.

Results describing effect modification by comorbidities are shown in Table 6. No significant differences across strata ($p < 0.20$) were noted when considering age as a modifying factor. In CHEERS, the average number of daily bowel movements at baseline was found to modify the association between major versus minor responses to symptoms and water exposure. Overall, those with two or more daily bowel movements at baseline had greater odds of severe symptoms associated with greater recreational water exposure compared to those with only one bowel movement per day at baseline. In NEEAR, having a previous GI condition or having any comorbid condition (previous GI condition,

Table 4 | Relationship between symptom severity and water exposure or water quality among NEEAR water recreators

Severity outcome	Exposure	ZINB Ratio[a] (95% CI)	Logistic regression Odds ratio[b] (95% CI)
Duration of GI symptoms			
$n = 16{,}386$	Water ingested vs. wading	0.89 (0.59, 1.33)	–
	Swimming vs. wading	0.97 (0.71, 1.34)	–
$n = 16{,}378$	Enterococci qPCR, 75th percentile	1.54 (1.04, 2.28)	–
$n = 16{,}378$	Enterococci culture, 75th percentile	1.31 (0.96, 1.78)	–
GI SDs			
$n = 16{,}386$	Water ingested vs. wading	0.99 (0.74, 1.32)	–
	Swimming vs. wading	1.05 (0.83, 1.31)	–
$n = 16{,}378$	Enterococci qPCR, 75th percentile	1.42 (1.10, 1.84)	–
$n = 16{,}378$	Enterococci culture, 75th percentile	1.18 (0.96, 1.45)	–
Total SDs[c]			
$n = 17{,}061$	Water ingested vs. wading	1.02 (0.85, 1.25)	–
	Swimming vs. wading	0.93 (0.81, 1.08)	–
$n = 16{,}868$	Enterococci qPCR, 75th percentile	1.16 (0.98, 1.38)	–
$n = 16{,}898$	Enterococci culture, 75th percentile	0.98 (0.85, 1.12)	–
Major vs. minor responses to symptoms[d]			
$n = 17{,}037$	Water ingested vs. wading	–	1.57 (1.27, 1.95)
	Swimming vs. wading	–	1.12 (0.95, 1.32)
$n = 16{,}842$	Enterococci qPCR, 75th percentile	–	1.12 (0.93,1.35)
$n = 16{,}842$	Enterococci culture, 75th percentile	–	1.00 (0.84, 1.17)

[a]Ratio refers to duration ratio or SDs ratio, control for beach as a fixed effect.
[b]Odds ratio evaluating odds of severe illness in exposed versus unexposed (reference group), control for beach as a fixed effect and household clustering.
[c]Includes GI and non-GI symptoms.
[d]ED or hospitalization, contact with HCP, take prescription, lost work or daily activities vs. OTC use only or no response.

asthma, or skin condition) modified the association between exposure and symptom severity (among all study participants, including those with no symptoms, GI symptoms only, and AGI). In general, the presence of comorbidities resulted in a stronger association with severity.

DISCUSSION

This study used a more detailed approach to characterize illness associated with water recreation by incorporating indicators of severity. Rather than considering illness to be a simple, dichotomous outcome, we made use of a continuum of symptom severity data. We observed a wide range of symptom severity among swimmers, waders, and incidental-contact water recreators, including those who did not meet the case definition of AGI. In general, most individuals who develop symptoms have mild and self-limiting symptoms; however, some individuals develop more severe symptoms that require use of the healthcare system and lost productivity. Indications of severity were common among those who had GI symptoms, but not necessarily AGI. Overall, qPCR measures of enterococci were associated with increased severity of symptoms among NEEAR participants (Table 4). The degree of water contact was associated with increased odds of reporting a major response to symptoms among both NEEAR and CHEERS participants (Tables 4 and 5).

To evaluate the semi-continuous severity outcomes, ZINB models were used in this analysis in order to take into account the excess zeros provided by participants that did not develop symptoms. Traditional negative binomial models were also evaluated, but were found to have poorer model fit according to the Akaike information

Table 5 | Relationship between symptom severity and water exposure or water quality among CHEERS water recreators

Severity outcome	Exposure	ZINB Ratio[a] (95% CI)	Logistic regression Odds ratio[b] (95% CI)
Duration of GI symptoms			
$n = 6{,}975$	Water ingested vs. no water contact	1.20 (0.59, 2.41)	–
	Body wetness vs. no water contact	1.16 (0.79, 1.68)	–
$n = 4{,}693$	F+ coliphage, 75th percentile	1.04 (0.64, 1.64)	–
$n = 3{,}854$	Enterococci culture, 75th percentile	0.83 (0.51, 1.34)	–
GI SDs			
$n = 6{,}975$	Water ingested vs. no water contact	1.03 (0.62, 1.72)	–
	Body wetness vs. no water contact	1.09 (0.84, 1.45)	–
$n = 4{,}693$	F+ coliphage, 75th percentile	1.15 (0.83, 1.59)	–
$n = 3{,}854$	Enterococci culture, 75th percentile	1.00 (0.70, 1.44)	–
Total SDs[c]			
$n = 7{,}129$	Water ingested vs. no water contact	1.19 (0.76, 1.87)	–
	Body wetness vs. no water contact	1.24 (0.96, 1.60)	–
$n = 4{,}687$	F+ coliphage, 75th percentile	1.11 (0.81, 1.52)	–
$n = 3{,}854$	Enterococci culture, 75th percentile	1.02 (0.72, 1.46)	–
Major vs. minor responses to symptoms[d]			
$n = 7{,}304$	Water ingested vs. no water contact	–	1.50 (0.98, 2.30)
	Body wetness vs. no water contact	–	1.29 (1.06, 1.57)
$n = 4{,}929$	F+ coliphage, 75th percentile	–	0.85 (0.67, 1.07)
$n = 4{,}094$	Enterococci culture, 75th percentile	–	0.95 (0.74, 1.22)

[a]Ratio refers to the duration ratio or SDs ratio calculated using ZINB.
[b]Odds ratio evaluating odds of severe illness in exposed versus the unexposed (reference group).
[c]Includes GI and non-GI symptoms.
[d]ED or hospitalization, contact with HCP, take prescription, lost work or daily activities vs. OTC use only or no response.

criterion (AIC). Details of these models, are found in the Supplementary Tables S4–S7. Additionally, both Poisson and zero-inflated Poisson models were also considered, but resulted in poor model fit (not shown).

The results of this analysis suggest that increased exposure to fecal indicators may be associated with more severe outcomes among swimmers in NEEAR, but not among incidental-contact recreators in CHEERS. We did however observe increased odds of major responses to symptoms when evaluating quartiles of F+ coliphage, but this was only limited to one quartile comparison (quartile 2 versus quartile 1) (Supplementary Table S3). This is consistent with the finding that the occurrence of GI illness was associated with water quality in NEEAR (Wade *et al.* 2006, 2008, 2010) but not in CHEERS (Dorevitch *et al.* 2015). It is possible that the greater water exposure experienced by swimmers (Dufour *et al.* 2006) in NEEAR compared to incidental-contact water recreators (Dorevitch *et al.* 2011) in CHEERS results in greater exposure and potential dose. Previous waterborne studies (Keene *et al.* 1994) and other outbreaks (Taylor *et al.* 1984; Glynn & Bradley 1992; Mertens *et al.* 2013) have indicated that a greater dose of microorganisms can be associated with greater severity of symptoms.

The majority of recent US studies have relied on a common case definition to describe the occurrence of GI illness among water recreators, but a few alternatives to describing the occurrence of illness have been used. Some studies have used a definition of the occurrence of diarrhea (Colford *et al.* 2007; Heaney *et al.* 2012; Arnold *et al.* 2013), while others have utilized alternate more or less stringent definitions of illness (Colford *et al.* 2007). Moving beyond the use of a yes/no case definition may have potential to generate more complete information regarding illness among water recreators in future studies.

Table 6 | Modification of the associations between severity and water exposure among all water recreators

Severity outcome	Interaction *p*-value	Exposure	Condition (modifier)	Stratum specific outcome
CHEERS				
Major vs. minor responses to symptoms[a]	0.025	Water ingested vs. no water contact	>2 daily bowel movements at baseline	OR = 4.00 (1.58, 10.14) $n = 22$
			2 daily bowel movements at baseline	OR = 2.00 (1.23, 3.26) $n = 82$
			<2 daily bowel movements at baseline	OR = 1.00 (0.55, 1.81) $n = 197$
	0.61	Body wetness only vs. no water contact	>2 daily bowel movements at baseline	OR = 1.48 (0.90, 2.35) $n = 369$
			2 daily bowel movements at baseline	OR = 1.36 (1.06, 1.75) $n = 1,397$
			<2 daily bowel movements at baseline	OR = 1.26 (0.99, 1.61) $n = 3,094$
NEEAR				
Major vs. minor responses to symptoms[a]	0.18	Water ingested vs. wading	Comorbid condition	OR = 1.88 (1.35, 2.62) $n = 564$
			No comorbid condition	OR = 1.43 (1.10, 1.85) $n = 1,814$
	0.18	Swimming vs. wading	Comorbid condition	OR = 1.28 (1.00, 1.65) $n = 2,750$
			No comorbid condition	OR = 1.03 (0.84, 1.27) $n = 8,006$
GI SDs	0.09	Water ingested vs. wading	Comorbid GI condition	SDs ratio = 3.00 (0.80, 11.39) $n = 30$
			No comorbid GI condition	SDs ratio = 0.93 (0.69, 1.26) $n = 2,346$
	0.19	Swimming vs. wading	Comorbid GI condition	SDs ratio = 1.89 (0.76, 4.61) $n = 239$
			No comorbid GI condition	SDs ratio = 1.01 (0.80, 1.27) $n = 10,504$
Total SDs[b]	0.006	Water ingested vs. wading	Comorbid condition	SDs ratio = 1.47 (1.06, 2.02) $n = 564$
			No comorbid condition	SDs ratio = 0.86 (0.68, 1.07) $n = 1,814$
	0.12	Swimming vs. wading	Comorbid condition	SDs ratio = 1.10 (0.86, 1.40) $n = 2,750$
			No comorbid condition	SDs ratio = 0.87 (0.73, 1.03) $n = 8,006$

[a]ED or hospitalization, contact with HCP, prescription medication use, lost work or daily activities vs. OTC use only or no response to illness.
[b]Includes GI and non-GI symptoms.

In contrast to the dichotomous illness classification used in prior studies, we observed that on either side of the dividing line between well and ill, a range of severity was observed. While those who met the case definition for AGI had on average higher durations of GI symptoms and more SDs, those not meeting the case definition also had appreciable severity of symptoms. Furthermore, considerable variability in severity was observed among those who met the case definition (Table 3).

The collection and analysis of responses to symptoms or use of the healthcare system may be more important for understanding the overall health impacts of exposure to fecally-contaminated recreational waters. For example, an individual may take an antiemetic to relieve symptoms of vomiting and nausea, or an anti-diarrheal agent to relieve symptoms of diarrhea. If these medications are effective in preventing vomiting and no more than two loose stools per 24 hours, the individuals, who clearly were symptomatic, would not be considered 'cases'. Thus, the use of the semi-continuous measures and responses to symptoms we assessed may provide more detailed and nuanced description of the short term health consequences of water recreation.

The current study had several strengths. First, the severity of symptoms was evaluated among two large cohort studies of water recreation with similar protocols. The studies were set in several US locations impacted by human fecal pollution and evaluated exposures in urban (Dorevitch *et al.* 2012) and less-urban environments (Wade *et al.* 2006, 2008, 2010). This analysis also evaluated severity using several severity metrics relating to different types of water recreation and varying degrees of water exposure within those types of recreation.

The results of this analysis should be considered in light of several important limitations. First, the ascertainment of severity relied on self-report. Furthermore, several metrics, including the duration of symptoms and SDs, relied on self-reported start and end dates of symptoms. The ability for participants to recall specific information regarding the date their symptoms began may be problematic, and could impact the accuracy of the duration estimates. However, we do not think that bias was introduced, in that swimmers, waders, and incidental-contact recreators, with varying exposure to microbes, would likely have comparable patterns in self-reporting symptom onset and resolution dates. Also, while calculating SDs in this analysis, we chose to weight more severe symptoms, such as vomiting and diarrhea, by a factor of two, while leaving less severe symptoms (nausea and stomachache) weighted by a factor of one. While highlighting the severity of individual symptoms (diarrhea, vomiting) has been suggested (Freedman *et al.* 2010), objectively derived weighting values have yet to be described. For that reason, we have no basis for assessing the accuracy of the weighting factors that we applied. In addition, the two epidemiology studies took place on waters impacted by fecal pollution. Therefore, the results of the analyses of water exposure or microbe density as a predictor of severity may not be generalizable to the users of waters not impacted by point sources of fecal pollution. In addition, we chose to evaluate GI symptoms developing within 3 days of recreation, as this time frame to development of symptoms has been previously shown to be the most strongly associated with water recreation (Dorevitch *et al.* 2012; Arnold *et al.* 2013). However, we could be underestimating overall severity by not including symptoms corresponding to pathogens or viruses with longer incubation periods.

Additionally, differences in telephone follow-up may account for the numbers who reported GI symptoms, but not AGI among CHEERS versus NEEAR recreators (Table 3). It is possible that in NEEAR, the individual responding for the entire household may not have been fully aware of all minor symptoms (stomachache, a half a day of nausea) experienced by the entire household, which may have been recognized by individual self-report in CHEERS. However, it is unclear if proxy reports would over- or underestimate these measures.

Others have found that outside of the context of water recreation, socioeconomic status can impact decisions to seek medical care (Adler *et al.* 1993; Stratmann 1999; Anderson 2007; Blackwell *et al.* 2009). We found that among CHEERS participants, median household income in the participants' home zip code was significantly higher ($p < 0.01$) among water recreators compared to non-water recreators. Furthermore, those who lived in zip codes with higher incomes were less likely to report indicators of severity in both NEEAR and CHEERS (Supplementary Tables S8 and S9, available with the online version of this paper). Potential socioeconomic differences should be further examined among water recreators compared to non-water recreators in future studies.

CONCLUSIONS

The severity of symptoms may be useful as a health outcome measure in future studies of water recreation. Evidence from this analysis indicates that the definition of illness used in recent studies results in some individuals with relatively low severity being included as cases of illness while some individuals with high severity are excluded. By examining the relationship between severity and water exposures, optimized definitions can be identified based on the resulting differences in symptom severity between water recreators and non-water recreators. Modeling environmental exposures as predictors of health outcomes might be improved if the burden of disease, which takes into account both the incidence and severity of symptoms, were studied as a health endpoint rather than simply looking at incidence.

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DISCLAIMER

The views expressed in this manuscript are those of the individual authors and do not necessarily reflect the views and policies of the US EPA. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

CONFLICT OF INTEREST

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