Infectious Diseases

A systematic review and meta-analysis of ambient temperature and diarrhoeal diseases

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Abstract

Background: Global climate change is expected to increase the risk of diarrhoeal diseases, a leading cause of childhood mortality. However, there is considerable uncertainty about the magnitude of these effects and which populations bear the greatest risks.

Methods: We conducted a systematic review using defined search terms across four major databases and, additionally, examined the references of 54 review articles captured by the search. We evaluated sources of heterogeneity by pathogen taxon, exposure measure, study quality, country income level and regional climate, and estimated pooled effect estimates for the subgroups identified in the heterogeneity analysis, using meta-analysis methods.

Results: We identified 26 studies with 49 estimates. Pathogen taxa were a source of heterogeneity. There was a positive association between ambient temperature and all-cause diarrhoea (incidence rate ratio (IRR) 1.07; 95% confidence interval (CI) 1.03, 1.10) and bacterial diarrhoea (IRR 1.07; 95% CI 1.04, 1.10), but not viral diarrhoea (IRR 0.96; 95% CI 0.82, 1.11). These associations were observed in low-, middle- and high-income countries. Only one study of protozoan diarrhoea was identified.

Conclusions: Changes in temperature due to global climate change can and may already be affecting diarrhoeal disease incidence. The vulnerability of populations may depend, in part, on local pathogen distribution. However, evidence of publication bias and the uneven geographical distribution of studies limit the precision and generalizability of the pooled estimates.

Key words: Ambient temperature, weather, diarrhoea, climate change, vulnerability
Introduction

Global climate change is expected to increase the risk of diarrhoeal diseases, the second leading cause of death in children under 5 years of age. Diarrhoea accounted for 3.6% of the global disease burden in 2010, with much of this burden concentrated in low-resource settings. Even modest changes in diarrhoea risk can yield large changes in morbidity and mortality.

Attempts to quantify the potential impacts of climate change on diarrhoea have been hampered by uncertainties regarding climate-disease relationships. Recent estimates of global health risk factors excluded climate change, because of the scarcity of empirical evidence regarding climate-disease relationships. Another study concluded that the greatest sources of uncertainty in projecting the impact of climate change on diarrhoeal diseases were due not to climate models but to gaps in scientific evidence linking temperature and diarrhoeal diseases. Reviews have evaluated the relationship between temperature and diarrhoea, focusing on specific pathogens and exposure pathways, but systematic review and quantitative synthesis are needed.

The complexity of diarrhoea aetiology and transmission makes evaluating the empirical relationships between diarrhoeal diseases and climatic factors challenging. Infectious diarrhoea can be caused by a range of pathogens whose relative importance varies regionally. Infection can be acquired through multiple exposure pathways including food, water, person-to-person contact and direct exposure to fecal waste—pathways linked to safe water and sanitation infrastructure. Host susceptibility also plays a key role in diarrhoeal diseases. Changes in ambient temperature, precipitation and the frequency of extreme weather events may alter the distribution, survival and virulence of diarrhoeal pathogens, change host exposure patterns and compromise infrastructure. Given this complexity, the effect of temperature on diarrhoeal diseases may not be uniform across all pathogens, host populations and environments.

Here, we present a comprehensive systematic review and meta-analysis of the literature describing the relationship between ambient temperature and diarrhoea. We synthesized the available literature, identified key gaps and evaluated sources of heterogeneity in an effort to advance our ability to predict the potential impacts of climate change on diarrhoeal disease and to highlight research needs.

Methods

Search strategy

As part of a larger systematic review of the relationship between temperature, precipitation and diarrhoeal diseases, we searched for the health outcome terms ‘diarrhoea’ and ‘diarrhea’, paired with climate terms: ‘climate change’, ‘temperature’, ‘rain*’, ‘precipitation’, ‘flood*’, ‘drought*’ or ‘sea surface temperature’, using PubMed, Embase, Web of Science and the Cochrane Collection on 26 November 2013. In addition, we searched the references of 54 review articles identified during the search for additional relevant articles. Test searches using pathogen-specific search terms indicated the inclusion of these additional terms was unlikely to alter the final selection of manuscripts. Figure 1 shows the search strategy.

Eligibility

Studies were included in this meta-analysis if: (i) the outcome measure was incidence or counts of diarrhoea, or a pathogen-specific diarrhoeal disease at a monthly or finer resolution; (ii) the exposure of interest was mean, maximum or minimum ambient temperature; (iii) the study included at least 1 continuous year of data to allow adjustment for seasonality and avoid analyses focused on a single temperature event; (iv) the parameter estimated was an incidence rate ratio (IRR) or it was possible to convert the estimate to an IRR expressing change in diarrhoea incidence per a 1°C increase in temperature; and (v) standard errors and/or confidence intervals were provided. Articles were

Key Messages

• The relationship between ambient temperature and diarrhoeal diseases is variable and this variability is due in part to pathogen taxon, based on a review of 26 manuscripts.
• Increases in ambient temperature were generally associated with increases in all-cause and bacterial diarrhoea.
• Increases in ambient temperature were not associated with increases in viral diarrhoea.
• There was insufficient evidence to evaluate relationships between ambient temperature and protozoan diarrhoea.
• The impact of climate change on diarrhoeal diseases may vary regionally due, in part, to spatial variability in the distribution of pathogens. More research is needed to understand how infectious disease risks due to climate change vary across other factors such as access to safe water and sanitation, demographics and local climate norms.
limited to English-language publications. Articles initially were screened by APW and RSG, and full-text articles were screened by two reviewers (EJC and APW or RSG).

Data extraction and quality scoring
Data extracted from each study include study location, exposures, outcomes and analytical methods. When regression coefficients were provided instead of IRRs, parameters were converted to IRRs using standard methods.13 Where multiple estimates were reported, Cochrane Collaboration guidelines14 determined the criteria for inclusion: we selected the final model as specified by the authors or, if a final model was not specified, the model with the greatest number of relevant covariates. Estimates for distinct geographical regions were extracted separately. In one manuscript,15 effect estimates were presented for three bacterial pathogens in one province and only one pathogen (Campylobacter) in the other. We extracted only the Campylobacter estimates to reduce publication bias and population overlap.

In order to evaluate the impact of study quality on pooled estimates, we adapted published instruments following standard guidelines.14,16,17 Our instrument included nine items assessing reporting quality, bias and external validity, with possible scores ranging from 0 (poor quality) to 10 (high quality) (see Supplementary data, available at IJE online). Each manuscript was scored by two independent reviewers (APW and RSG) and discrepancies were resolved jointly.

Meta-analysis
We evaluated heterogeneity in the relationships between temperature and diarrhoea, using forest plots and the Mantel–Haenszel test for heterogeneity.14 We then analysed sources of heterogeneity using a set of five
variables selected a priori, related to diarrhoea aetiology (pathogen taxon), study design (exposure measure and study quality) and population vulnerability. Measures of vulnerability included country income level based on World Bank classifications of low- or middle-income countries (LMIC) vs high-income countries (HIC) and the predominant climate at each study location (Koppen climate classifications). Because only two studies were conducted in arid regions, both in Lima, Peru, we collapsed climate classification into three categories: tropical/ arid, temperate and cold/polar. We classified two studies that pooled data from multiple countries as tropical, because the majority of sites included in these studies were tropical. We used a Monte Carlo permutation test to evaluate whether the above variables explain variability in the effect estimates, running 10 000 permutations using both univariate and multivariate models, and presenting p-values that account for multiple hypothesis testing. Because only one study of protozoan diarrhoea was identified, we excluded this from this heterogeneity analysis.

Meta-analysis was used to estimate pooled effects by variables identified in the heterogeneity analysis. Mantel-Haenszel tests indicated significant heterogeneity within each subgroup (P < 0.001), so pooled effects were estimated using DerSimonian and Laird random effects models. We conducted a sensitivity analysis, estimating pooled effect estimates by diarrhoeal pathogen taxon, using robust variance estimate meta-analysis methods, to account for potential correlation of estimates within the same publication. We assumed a within-study correlation of 0.1, but evaluated estimates at rho = 0.1, 0.3, 0.5, 0.7 and 0.9 and found that point estimates and confidence intervals varied by < 0.001 across these values. We used the robust variance estimate with small sample size correction; however, estimates using this method are unstable when the number of clusters is limited, so we conducted this sensitivity analysis only on the highest level of stratification. Due to the large number of studies of bacterial diarrhoea captured, we repeated the heterogeneity analysis on these studies using the remaining four covariates.

We used the metan, metareg and robmeta packages in Stata version 13.1. Following previous work, we defined x as the change in the rate ratio of diarrhoea for a 1°C increase in ambient temperature, using the pooled IRR estimates from the meta-analysis. Publication bias was assessed by inspecting funnel plots for asymmetry, which suggests ‘small study bias’.

Results
We identified 26 manuscripts that met our inclusion criteria (Table 1) and 49 estimates of the relationship between ambient temperature and diarrhoea within these manuscripts (Figure 2). Study locations included low-, middle- and high-income countries and all six inhabited continents; however, research was concentrated in three countries: Bangladesh (five manuscripts), Australia (five) and the UK (four) (Figure 3).

Sources of heterogeneity
There was considerable heterogeneity across the 49 estimates (P < 0.001). Pathogen taxa were the only variables that explained heterogeneity (P = 0.020 for viral diarrhoea in multivariate analyses, P < 0.001 in univariate analyses).

All-cause diarrhoea
We identified ten estimates from seven manuscripts of the relationship between all-cause diarrhoea and temperature. Pooled estimates indicated a positive association between ambient temperature and diarrhoea (Table 2). Pooled estimates based on maximum and minimum temperature were more variable than estimates based on mean ambient temperature, though four out of five estimates were derived from a single study that had one of the lowest quality scores. Excluding that study yielded minimal change in the pooled estimate (IRR = 1.06, 95% CI 1.03, 1.09).

Bacterial diarrhoea
We identified 30 estimates from 12 manuscripts of the relationship between temperature and bacterial diarrhoea, including non-typhoidal Salmonella sp. (20), Campylobacter (5), Vibrio cholerae (3), Salmonella typhi (1) and Shigella (1). Pooled estimates indicated a significant positive association between ambient temperature and bacterial diarrhoea.

Pooled estimates were stable across mean, maximum and minimum temperature, but were modestly higher in lower quality studies, studies conducted in LMIC and in tropical climates (Figure 4). Heterogeneity analysis indicated that study quality and climate were sources of variability in multivariate models (P = 0.055 and P = 0.085, respectively) although these findings may be due to chance.

Protozoan diarrhoea
Only one estimate of the relationship between temperature and a protozoan pathogen, Cryptosporidium, was identified. This study showed a significant positive association between ambient temperature and cryptosporidiosis.

Viral diarrhoea
We identified eight estimates from six manuscripts of the relationship between temperature and viral diarrhoea, including rotavirus (seven) and norovirus (one), all with mean ambient temperature as the exposure. All but one
Table 1. Summary of the 26 publications included in the meta-analysis

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Location</th>
<th>Study period</th>
<th>Population</th>
<th>Ages</th>
<th>Outcome</th>
<th>Taxonomic class</th>
<th>Exposure definition</th>
<th>Statistical model</th>
<th>Temporal lags</th>
<th>Threshold</th>
<th>Resolution</th>
<th>Climate group</th>
<th>Income group</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ali (2013)</td>
<td>Matlab, Bangladesh</td>
<td>1988–2001</td>
<td>4,157 cases</td>
<td>All</td>
<td>Cholera cases presenting to treatment centres</td>
<td>Bacterial</td>
<td>Minimum temperature</td>
<td>Seasonal auto-regressive integrated moving average (SARIMA) model adjusted for sea surface temperature, season, autocorrelation</td>
<td>None</td>
<td>None</td>
<td>Monthly</td>
<td>A</td>
<td>Low</td>
<td>8</td>
</tr>
<tr>
<td>Bi (2008)</td>
<td>Adelaide and Brisbane, Australia</td>
<td>1990–2005</td>
<td>34,908 cases</td>
<td>All</td>
<td>Reported, lab-confirmed <em>Campylobacter</em></td>
<td>Bacterial</td>
<td>Maximum temperature</td>
<td>Poisson regression model adjusted for rainfall (Adelaide only), humidity (Brisbane only), long-term trends (Brisbane only), season, autocorrelation</td>
<td>9 weeks, Adelaide; 6 weeks, Brisbane</td>
<td>None</td>
<td>Weekly</td>
<td>C</td>
<td>High</td>
<td>8</td>
</tr>
<tr>
<td>Britton (2010)</td>
<td>New Zealand</td>
<td>1965–2006</td>
<td>NA</td>
<td>All</td>
<td>Reported <em>Salmonella</em></td>
<td>Bacterial</td>
<td>Mean temperature</td>
<td>Negative binomial regression model adjusted for outbreak periods, long-term trends, season, autocorrelation</td>
<td>None</td>
<td>None</td>
<td>Monthly</td>
<td>C</td>
<td>High</td>
<td>6</td>
</tr>
<tr>
<td>Checkley (2000)</td>
<td>Lima, Peru</td>
<td>1993–98</td>
<td>57,331 cases</td>
<td>&lt; 10</td>
<td>Diarrhoea admissions at a children’s hospital</td>
<td>All-cause</td>
<td>Mean temperature</td>
<td>Poisson regression</td>
<td>37 days</td>
<td>None</td>
<td>Daily</td>
<td>B</td>
<td>Upper middle</td>
<td>7</td>
</tr>
<tr>
<td>Chou (2010)</td>
<td>Taiwan</td>
<td>1996–2007</td>
<td>1.2 million cases</td>
<td>0–64</td>
<td>Hospital admissions for diarrhoea from National Health Insurance Research database</td>
<td>All-cause</td>
<td>Maximum temperature</td>
<td>Poisson regression model adjusted for extreme rainfall, humidity, long-term trends, season, autocorrelation</td>
<td>1 month</td>
<td>None</td>
<td>Monthly</td>
<td>C</td>
<td>High</td>
<td>8</td>
</tr>
<tr>
<td>Dewan (2013)</td>
<td>Dhaka, Bangladesh</td>
<td>2005–09</td>
<td>4,355 cases</td>
<td>All</td>
<td>Lab-confirmed typhoid cases admitted to 11 hospitals</td>
<td>Bacterial</td>
<td>Mean temperature</td>
<td>Poisson regression model adjusted for rainfall, river level, holidays, long-term trends, season, autocorrelation</td>
<td>0–4 weeks</td>
<td>None</td>
<td>Weekly</td>
<td>A</td>
<td>Low</td>
<td>9</td>
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<tr>
<td>D’Souza (2004)</td>
<td>Five cities in Australia</td>
<td>1991–2001</td>
<td>27,632 cases</td>
<td>All</td>
<td>Reported <em>Salmonella</em></td>
<td>Bacterial</td>
<td>Mean temperature</td>
<td>Negative binomial regression model adjusted for outbreaks and long-term trends, season, autocorrelation</td>
<td>1 month</td>
<td>None</td>
<td>Monthly</td>
<td>C</td>
<td>High</td>
<td>8</td>
</tr>
<tr>
<td>D’Souza (2008)</td>
<td>Brisbane, Canberra and Melbourne, Australia</td>
<td>1993–2003</td>
<td>12,816 cases</td>
<td>&lt; 5</td>
<td>Hospital admissions for rotavirus from state health department records</td>
<td>Viral</td>
<td>Mean temperature</td>
<td>Negative binomial regression model adjusted for humidity, long-term trends, season, autocorrelation</td>
<td>1 week</td>
<td>None</td>
<td>Weekly</td>
<td>C</td>
<td>High</td>
<td>9</td>
</tr>
<tr>
<td>Fleury (2006)</td>
<td>Newfoundland-Labrador (NL) and Alberta, Canada</td>
<td>1992–2000</td>
<td>2,931 cases</td>
<td>All</td>
<td>Reported, lab-confirmed <em>Campylobacter</em></td>
<td>Bacterial</td>
<td>Mean temperature</td>
<td>Poisson regression model adjusted for holidays, health region, long-term trends, season, autocorrelation</td>
<td>1 week</td>
<td>−10°C</td>
<td>Alberta, &gt; 0°C</td>
<td>D</td>
<td>High</td>
<td>9</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Location</th>
<th>Study period</th>
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<th>Temporal lags</th>
<th>Threshold</th>
<th>Resolution</th>
<th>Climate group</th>
<th>Income group</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashizume (2007)</td>
<td>Dhaka, Bangladesh</td>
<td>1996–2002</td>
<td>12 182 cases</td>
<td>All</td>
<td>Non-cholera diarrhoea cases presenting to ICDDR,B Dhaka Hospital</td>
<td>All-cause</td>
<td>Mean temperature</td>
<td>Poisson regression model adjusted for rainfall, holidays, long-term trends, season, autocorrelation</td>
<td>0–4 weeks</td>
<td>None</td>
<td>Weekly</td>
<td>A</td>
<td>Low</td>
<td>10</td>
</tr>
<tr>
<td>Hashizume (2008)</td>
<td>Dhaka, Bangladesh</td>
<td>1996–2001</td>
<td>3 113 cases</td>
<td>All</td>
<td>Lab-confirmed rotavirus diarrhoea presenting to ICDDR,B Dhaka Hospital</td>
<td>Viral</td>
<td>Mean temperature</td>
<td>Poisson regression model adjusted for relative humidity, river level, holidays, long-term trends, season, autocorrelation</td>
<td>0–4 weeks</td>
<td>&gt;29°C</td>
<td>Weekly</td>
<td>A</td>
<td>Low</td>
<td>9</td>
</tr>
<tr>
<td>Jagai (2012)</td>
<td>Six countries in South Asia</td>
<td>1976–2009</td>
<td>47 time series from 39 studies</td>
<td>All</td>
<td>Rotavirus z-score</td>
<td>Viral</td>
<td>Temperature z-score</td>
<td>Linear mixed effects model adjusted for precipitation, vegetation index, distance from the equator</td>
<td>1 month</td>
<td>None</td>
<td>Monthly</td>
<td>A/B/C</td>
<td>Low and lower middle</td>
<td>7</td>
</tr>
<tr>
<td>Lama (2004)</td>
<td>Lima, Peru</td>
<td>1991–98</td>
<td>40 020 cases</td>
<td>13</td>
<td>Emergency department admissions for acute diarrhoea</td>
<td>All-cause</td>
<td>Mean temperature</td>
<td>Log-linear regression model with an interaction term between temperature and cholera in the community</td>
<td>None</td>
<td>None</td>
<td>Monthly</td>
<td>B</td>
<td>Upper middle</td>
<td>6</td>
</tr>
<tr>
<td>Levy (2009)</td>
<td>Global tropics</td>
<td>1974–2005</td>
<td>26 studies</td>
<td>All</td>
<td>Rotavirus cases</td>
<td>Viral</td>
<td>Mean temperature</td>
<td>Poisson regression model adjusted for study, within study correlation and autocorrelation</td>
<td>None</td>
<td>None</td>
<td>Monthly</td>
<td>Multiple</td>
<td>Multiple</td>
<td>7</td>
</tr>
<tr>
<td>Lopman (2009)</td>
<td>England and Wales</td>
<td>1993–2006</td>
<td>3 210 cases</td>
<td>All</td>
<td>Reported, lab-confirmed norovirus</td>
<td>Viral</td>
<td>Mean temperature</td>
<td>Poisson regression adjusted for relative humidity, holidays and weekends, epidemic season, use of improved diagnostics, population immunity, long-term trends, season, autocorrelation</td>
<td>49 days</td>
<td>None</td>
<td>Daily</td>
<td>C</td>
<td>High</td>
<td>9</td>
</tr>
<tr>
<td>Luque Fernandez (2009)</td>
<td>Lusaka, Zambia</td>
<td>2003–06</td>
<td>13 069 cases</td>
<td>All</td>
<td>Cholera cases at cholera isolation centres</td>
<td>Bacterial</td>
<td>Maximum temperature</td>
<td>Poisson regression adjusted for rainfall, season, autocorrelation</td>
<td>6 weeks</td>
<td>None</td>
<td>Weekly</td>
<td>C</td>
<td>Lower middle</td>
<td>8</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Ref.</th>
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<th>Study period</th>
<th>Population</th>
<th>Ages</th>
<th>Outcome</th>
<th>Taxonomic class</th>
<th>Exposure definition</th>
<th>Statistical model</th>
<th>Temporal lags (^{a})</th>
<th>Threshold</th>
<th>Resolution</th>
<th>Climate group (^{b})</th>
<th>Income group (^{c})</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onozuka (2010)</td>
<td>Fukuoka, Japan</td>
<td>1999–2007</td>
<td>422 176 cases</td>
<td>All</td>
<td>Infectious gastroenteritis at 120 sentinel medical institutions</td>
<td>All-cause</td>
<td>Mean temperature</td>
<td>Poisson regression adjusted for relative humidity, long-term trends, season, autocorrelation</td>
<td>0-4 weeks</td>
<td>None</td>
<td>Weekly</td>
<td>D</td>
<td>High</td>
<td>9</td>
</tr>
<tr>
<td>Seidu (2013)</td>
<td>Northern Ghana</td>
<td>2008–09</td>
<td>2664 participants</td>
<td>All</td>
<td>Self-reported diarrhoea from bi-weekly interviews</td>
<td>All-cause</td>
<td>Maximum, minimum temperature</td>
<td>Poisson regression model adjusted for maximum and minimum rainfall, maximum and minimum temperature, 1-2 bi-weeks earlier, season, autocorrelation</td>
<td>None</td>
<td>None</td>
<td>Bi-weekly</td>
<td>A</td>
<td>Lower middle</td>
<td>5</td>
</tr>
<tr>
<td>Singh (2001)</td>
<td>Fiji</td>
<td>1978–98</td>
<td>NA</td>
<td>Infants</td>
<td>Reported diarrhoea</td>
<td>All-cause</td>
<td>Mean temperature</td>
<td>Poisson regression model adjusted for rainfall, season</td>
<td>1 month</td>
<td>None</td>
<td>Monthly</td>
<td>A</td>
<td>Upper</td>
<td>5</td>
</tr>
<tr>
<td>Traerup (2011)</td>
<td>Tanzania</td>
<td>1998–2004</td>
<td>NA</td>
<td>All</td>
<td>Reported cholera</td>
<td>Bacterial</td>
<td>Maximum temperature</td>
<td>Negative binomial regression adjusted for long-term trends, drought</td>
<td>None</td>
<td>None</td>
<td>Monthly</td>
<td>A</td>
<td>Low</td>
<td>7</td>
</tr>
<tr>
<td>Zhang (2008)</td>
<td>Jinan, China</td>
<td>1987–2000</td>
<td>60 905 cases</td>
<td>All</td>
<td>Reported hospital cases of bacillary dysentery</td>
<td>Bacterial</td>
<td>Maximum temperature</td>
<td>SARIMA model adjusted for season and autocorrelation</td>
<td>1 month</td>
<td>None</td>
<td>Monthly</td>
<td>D</td>
<td>Upper middle</td>
<td>6</td>
</tr>
<tr>
<td>Zhang (2010)</td>
<td>Brisbane and Townsville, Australia</td>
<td>1990–2005</td>
<td>6464 cases</td>
<td>All</td>
<td>Reported lab-confirmed Salmonella</td>
<td>Bacterial</td>
<td>Maximum, minimum temperature</td>
<td>Poisson regression adjusted for rainfall, long-term trends, season, autocorrelation</td>
<td>2 weeks (Brisbane); none (Townsville)</td>
<td>None</td>
<td>Weekly (Brisbane), monthly (Townsville)</td>
<td>A/C</td>
<td>High</td>
<td>8</td>
</tr>
</tbody>
</table>

NA, not available.

\(^{a}\)Lag between exposure and outcome included in the final model.

\(^{b}\)Climate categories are based on Koppen-Geiger climate classification where A is tropical, B is arid, C is temperate, D is cold and E is polar.

\(^{c}\)Categories are based on 2012 gross national income per capita.

\(^{d}\)The authors reported 6282 cases of Salmonella, 1743 cases of Campylobacter and 9664 cases of enteropathogenic E. coli in Alberta, and 986 cases of Salmonella, 1188 cases of Campylobacter and 0 cases of enteropathogenic E. coli in Newfoundland-Labrador. However, the only reported effect estimates available for both provinces described the relationship between Campylobacter and temperature (the authors reported a non-significant association between temperature and Salmonella in Newfoundland-Labrador, without providing an effect estimate). We therefore restricted the meta-analysis to Campylobacter in the two provinces to reduce publication bias and population overlap.

\(^{e}\)Except Poland (biweekly), Estonia and Slovak Republic (monthly).

\(^{f}\)Estimates included in this analysis were estimates of the association between temperature and diarrhoea when cholera was not present in the community.

\(^{g}\)Models fit separately for communities that apply fecal sludge and communities that do not. Autoregressive terms were only included in the former model.
Figure 2. Forest plot showing 49 estimates of the incidence rate ratio (IRR) and 95% confidence Interval (CI) from the 26 studies included in the meta-analysis, by pathogen taxon.
Figure 3. Map displaying the location of studies included in the meta-analysis, by country. The locations from one study that included data from more than 10 countries are excluded from the map. World shape file is from the GADM database of Global Administrative Areas.

Table 2. Pooled effect estimates of the relationship between ambient temperature and diarrhoeal diseases by pathogen taxon

<table>
<thead>
<tr>
<th>Pathogen Taxon</th>
<th>No. estimates</th>
<th>No. papers</th>
<th>Unadjusted$^a$</th>
<th>Adjusted$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IRR (95% CI)</td>
<td>Alpha$^c$ (95% CI)</td>
</tr>
<tr>
<td>All-cause diarrhoea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All exposures</td>
<td>10</td>
<td>7</td>
<td>1.05 (1.01, 1.09)</td>
<td>0.05 (0.01, 0.08)</td>
</tr>
<tr>
<td>Mean temperature</td>
<td>5</td>
<td>5</td>
<td>1.07 (1.04, 1.09)</td>
<td>0.07 (0.04, 0.09)</td>
</tr>
<tr>
<td>Bacterial diarrhoea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All exposures</td>
<td>30</td>
<td>12</td>
<td>1.07 (1.05, 1.08)</td>
<td>0.06 (0.05, 0.08)</td>
</tr>
<tr>
<td>Mean temperature</td>
<td>20</td>
<td>6</td>
<td>1.07 (1.05, 1.08)</td>
<td>0.06 (0.05, 0.08)</td>
</tr>
<tr>
<td>Protozoan diarrhoea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All exposures</td>
<td>1</td>
<td>1</td>
<td>1.48 (1.07, 2.05)</td>
<td>0.48 (0.00, 0.96)</td>
</tr>
<tr>
<td>Mean temperature</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral diarrhoea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean temperature</td>
<td>8</td>
<td>6</td>
<td>0.95 (0.90, 1.00)</td>
<td>−0.05 (−0.10, 0.00)</td>
</tr>
</tbody>
</table>

$^a$Estimated using random effects model of DerSimonian and Laird.25
$^b$Estimated using robust variance estimation to account for correlation of estimates from the same manuscript. Not calculated for all-cause diarrhoea and mean temperature because each estimate is from a different manuscript. Not calculated for protozoan diarrhoea because only one estimate was available.
$^c$Defined as the proportional change in the rate ratio of diarrhoea for a 1°C change in ambient temperature.
estimate indicated a significant negative association, but the confidence intervals of the pooled estimates included the null. The one study with a positive effect employed a threshold analysis where a positive relationship was observed above $29^\circ C$. When this study was excluded, pooled estimates were further from the null (unadjusted IRR 0.93, 95% CI 0.88, 0.98; adjusted IRR = 0.91, 95% CI 0.84, 0.99).

Publication bias
Funnel plot asymmetry was observed for studies of bacterial and viral diarrhoeal pathogens, with a greater than expected number of smaller studies showing positive (bacterial) and negative (viral) outcomes than expected (Figure S1, see Supplementary data available at IJE online).

Discussion
We found considerable heterogeneity in estimated associations between ambient temperature and diarrhoeal diseases, and this variability was explained, in part, by pathogen taxon. Pooled estimates from 26 studies indicated a significant positive association between temperature and both all-cause and bacterial diarrhoea, but not between temperature and viral diarrhoea. These associations were observed in low-, middle- and high-income countries, suggesting that temperature can affect diarrhoea incidence across a range of conditions. However, the concentration of studies in a few countries and evidence of publication bias raises questions about the generalizability and precision of the pooled estimates. We identified only one study of protozoan diarrhoea that met our inclusion criteria, limiting our ability to evaluate relationships between temperature and this taxon. This is a key gap in the literature, as *Cryptosporidium* is a major cause of diarrhoea in children and immune-compromised populations.

Our findings offer an important advance in estimating the potential change in diarrhoeal disease burden attributable to climate change under different emissions scenarios. Using a cumulative risk assessment framework, climate-attributable disease burden depends on underlying disease rates, projected climatic changes and climate-disease risk parameters, represented here by $\alpha$. Our findings suggest that assuming a single, fixed value for $\alpha$ is not appropriate. In this study, we found $\alpha$ varies by pathogen taxon. Climate-diarrhoea risk parameters may vary across other parameters beyond the scope of this study, such as individual pathogens, exposure routes and access to water and sanitation infrastructure. Variability in $\alpha$ for diarrhoeal pathogens may also be explained, in part, by regional climate: Our analysis of bacterial diarrhoea suggests that the association between temperature and bacterial diarrhoea was higher in tropical climates, a phenomenon that warrants further evaluation.
Differential risk by climate type may be attributable to differences in pathogen distribution and/or underlying local vulnerabilities. If climate-risk parameters do vary, future climate-attributable diarrhoea disease burden may depend not just on future emission scenarios, but also on changes in socioeconomic and demographic patterns and on public health interventions, as has been demonstrated for malaria and waterborne diseases.

Based on the above cumulative risk assessment model, climate-attributable disease burden will be greatest in populations with an already high diarrhoea burden, particularly due to bacterial infections, and in areas with large increases in ambient temperature. Tropical, low-resource settings may bear a triple vulnerability profile due to the higher underlying diarrhoea rates, unprecedented future ambient temperatures and possibly greater temperature-diarrhoea risk parameters in these areas.

Limitations

We found evidence of publication bias, including small study publication bias, and of modestly stronger effect estimates in lower quality studies of bacterial diarrhoea. Both may indicate that estimates are inflated away from the null. Most of the studies we captured were secondary data analyses, which may be prone to a focus on significant findings. In our broader systematic review, we found that manuscripts with multiple effect estimates were more likely to include non-significant findings (unpublished data). In this meta-analysis, the only non-significant estimates were from a study that included multiple effects estimates. The inclusion of multiple estimates from the same studies may help mitigate publication bias. Whereas this has the potential to introduce correlation between estimates that, if not accounted for, may introduce bias, inference did not change when we used robust variance estimation models to account for within-study correlation. The publication of estimates that contradict the findings of similar studies, the fact that many studies drew from large, long-term datasets and the consistency of results across research groups, study designs and geographical locations bolsters confidence in this meta-analysis.

As has been done previously, we assumed a constant change in diarrhoea risk for every 1°C increase in temperature. The true relationship between temperature and diarrhoeal pathogens may be more complex. Fifteen estimates in our meta-analysis were based on threshold models, which account for non-linear exposure-response relationships by assuming linearity only above or below a given threshold. With two exceptions, threshold models included in our meta-analysis were based on data from temperate climates with lower thresholds, ranging from -10 to 14°C, suggesting that linear exposure-response relationships may be most appropriate for warmer temperature ranges. Additionally, our estimates of temperature-diarrhoea relationships are limited to the range of observable temperature data under current climate conditions. Although this may be sufficient for near-term predictions of climate-attributable health impacts, some scenarios suggest that temperatures in the tropics will exceed currently observed ranges with consequent health impacts that are difficult to predict. Global climate change will impact on not only temperature but also precipitation patterns, with implications for diarrhoeal diseases that we explore elsewhere.

The studies we captured in our meta-analysis are studies of association. A causal relationship between temperature and diarrhoeal diseases may be due in part to environmental factors, such as the impact of temperature on pathogen survival and reproduction in environmental media, or temperature-mediated virulence of pathogens. It is also possible that temperature-related behavioural or demographic patterns may drive these relationships, as has been suggested for viral diarrhoea. Behavioural and demographic seasonal factors might confound the relationship between ambient temperature and disease detection; however, many of the analyses captured in our study adjusted for season.

Future research

Our analysis offers a step towards understanding variability in temperature-diarrhoea risk parameters. Further research to characterize how the impact of changing temperature varies by pathogen and by known risk factors should be a priority, as it could improve our ability to identify high-risk populations and to prioritize adaptation targets. Large, multinational datasets that capture pathogen-specific diarrhoea could allow for further evaluation of variability in parameter estimates across such factors. Mechanistic transmission models, that integrate parameters from epidemiological and experimental studies, baseline conditions and future climate predictions, can also be used to evaluate the sensitivity of climate-attributable disease estimates to uncertainties in parameter estimates, highlighting future priority research areas. Quantitative analysis is also needed to understand the relationship between protozoan diarrhoea and ambient temperature, particularly in LMICs. The one study we identified and most of the studies identified in a recent review and meta-analysis, showed a positive association, but most of the work to date has been conducted in HICs, making it difficult to generalize these findings.

Conclusions

Studies conducted in Peru during an El Niño event in the 1990s provided early epidemiological evidence of the
potential for temperature anomalies to alter diarrhoea patterns. Twenty years later, our synthesis of 26 studies shows rising temperatures due to global climate change can and may already be affecting population health through increased risk of diarrhoeal diseases, particularly bacterial diarrhoea. Populations in tropical settings may be particularly vulnerable. Studies that evaluate heterogeneities in risk are needed to evaluate adaptation and mitigation measures in order to prevent delays or, worse, reversals of progress in reducing diarrhea disease burden.

Supplementary Data
Supplementary data are available at IJE online.

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