TITLE: Temperature impacts on dengue incidence are nonlinear and mediated by climatic and socioeconomic factors

RUNNING TITLE: Nonlinear temperature impacts on dengue

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49 **ABSTRACT**

50 Temperature can influence mosquito-borne diseases like dengue. These effects are expected to

51 vary geographically and over time in both magnitude and direction and may interact with other

52 environmental variables, making it difficult to anticipate changes in response to climate change.

53 Here, we investigate global variation in temperature–dengue relationship by analyzing published

54 correlations between temperature and dengue and matching them with remotely sensed climatic

55 and socioeconomic data. We found that the correlation between temperature and dengue was

56 most positive at intermediate (near 24°C) temperatures, as predicted from the thermal biology of

57 the mosquito and virus. Positive temperature–dengue associations were strongest when

58 temperature variation and population density were high and decreased with infection burden and

59 rainfall mean and variation, suggesting alternative limiting factors on transmission. Our results

60 show that while climate effects on diseases are context-dependent they are also predictable from

61 the thermal biology of transmission and its environmental and social mediators.

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INTRODUCTION

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69   Some infectious diseases are sensitive to changes in temperature (Lafferty 2009; Rohr *et*

70   *al.* 2011; Altizer *et al.* 2013; Lafferty & Mordecai 2016). This is most likely for pathogens

71   transmitted from ectothermic hosts or vectors and/or temperature-sensitive infectious stages in

72   the environment (Molnár *et al.* 2017). The dynamics and distributions of many diseases are

73   predicted to alter with climate change (IPCC AR6 WG2 report 2022), with effects on human

74   illness (Zhou *et al.* 2004), food security (Chakraborty & Newton 2011), and wildlife

75   conservation (Cohen *et al.* 2019). Accurately predicting the effects of temperature change on

76   infectious diseases requires understanding the impact of nonlinearity and the other factors that

77   mediate the impact of temperature on disease systems.

78

79   Temperature can increase or decrease biological rates and processes related to disease

80   transmission depending on the context; this type of nonlinearity makes predicting changes in

81   infectious disease with climate change difficult. The functional traits of organisms that contribute

82   to disease transmission—such as rates of development, activity, and fecundity and probabilities

83   of survival and reproduction—typically have hump-shaped responses to temperature, increasing

84   from zero at a critical thermal minimum up to an optimal temperature then declining to zero at a

85   critical thermal maximum (i.e., thermal performance curves; Angilletta 2009; Dell *et al.* 2011;

86   Amarasekare & Savage 2012; Mordecai *et al.* 2019). As a result, population and community-

87   level processes, including population dynamics (Savage *et al.* 2004), disease transmission

88   (Molnár *et al.* 2013), and trophic interactions (O'Connor *et al.* 2011; Dell *et al.* 2014), also tend

89   to respond nonlinearly to temperature, integrating influences of temperature on multiple life

90   stages and organisms. Thus, the observed effects of temperature on ecological processes can

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91   appear idiosyncratic, changing in direction and magnitude and becoming more or less apparent

92   under differing circumstances, belying general predictions for how ecosystems respond to

93   climate change (Hoos & Harley 2021).

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95   To understand this apparent context-dependence in how temperature affects disease

96   transmission, it may be beneficial to consider the temperature–disease relationships at a more

97   local scale. Rather than considering a full nonlinear response of disease transmission across a

98   large temperature range, we can instead consider the rate of change in disease with respect to

99   temperature—which may vary across ecological settings—to link locally-determined

100   relationships across places and times. For example, we may expect that local temperature–

101   disease relationships will be weak at the cold end of a thermal performance curve describing

102   disease transmission or incidence versus temperature, strongly positive where the slope of the

103   curve is highest, and zero or weak at the optimal temperature of the curve. Whether temperature

104   increases, decreases, or has no effect on disease transmission is therefore predicted to depend on

105   the local average temperature and its range.

106

107   In addition to the direct effects of temperature on disease transmission, other climatic and

108   non-climatic factors may mediate local temperature effects. For example, factors such as rainfall,

109   drought, snow, humidity, or local variability in temperature may interact with or modify the

110   impacts of mean temperature on disease. In particular, because body temperature and water

111   regulation are tightly linked organismal processes, rainfall and temperature often jointly

112   determine habitat availability and organismal performance (Rozen-Rechels *et al.* 2019), as has

113   been shown for juvenile Ixodid ticks when seeking hosts (Berger *et al.* 2014; Leal *et al.* 2020).

114   Local temperature variability can also play a mediating role via nonlinear averaging, in which

115   organismal performance, and resulting population and community processes at realized

116   temperatures, differ from what would be predicted at constant mean temperatures (Paaijmans *et*

117   *al.* 2009, 2010; Bernhardt *et al.* 2018). Notably, more variable temperature tends to rescue

118   disease transmission when it is cold and impair transmission when it is warm. Beyond climatic

119   effects, socioeconomic and anthropogenic factors impact ecological systems through processes

120   such as land conversion, wildlife trade and consumption, and the introduction of invasive

121   species, which drive shifts in biodiversity, resource availability, and species distributions (Mack

122   *et al.* 2000; Krkošek *et al.* 2007; Hendershot *et al.* 2020; Glidden *et al.* 2021). For diseases, these

123   and other socioeconomic factors such as vector control, hygiene, and healthcare can alter the

124   suitability of a location for disease transmission and opportunities for contacts among hosts

125   and/or vectors. Effects of temperature on disease are most detectable when conditions are

126   otherwise suitable for transmission, and may be dampened when other key requirements like host

127   and vector presence and contact are not met.

128

129   The net effects of nonlinearity and other factors mediating temperature impacts on

130   disease will have consequences for human health, especially for vector-borne diseases. In

131   particular, dengue is a climate-sensitive, tropical and subtropical disease caused by a flavivirus

132   (DENV) primarily transmitted by female *Aedes aegypti* mosquitoes; it causes 100-400 million

133   cases every year (WHO 2021) and cases have been increasing dramatically both regionally and

134   globally over the last three decades (Stanaway *et al.* 2016). Notably, since mosquitoes and the

135   parasites they harbor are ectotherms, temperature can influence multiple stages of the mosquito

136   life cycle and transmission cycle, affecting the distribution and dynamics of disease (Liu-

137   Helmersson *et al.* 2014; Morin *et al.* 2015; Wesolowski *et al.* 2015; Mordecai *et al.* 2017).

138   Previous research has used a combination of experiments and mathematical modeling to first

139   isolate the effects of temperature on different mosquito and pathogen traits (e.g., DENV

140   development rate within the mosquito, mosquito lifespan and fecundity) and then combine these

141   processes to understand how potential transmission rates vary across temperature (Lambrechts *et*

142   *al.* 2011; Liu-Helmersson *et al.* 2014; Wesolowski *et al.* 2015; Huber *et al.* 2018; Caldwell *et al.*

143   2021). This has provided specific predictions for how temperature affects dengue transmission in

144   the field: small increases in temperature should increase transmission up to the optimal

145   temperature of 29°C, after which increases in temperature should decrease transmission

146   (Mordecai *et al.* 2017). The greatest relative increase in transmission per degree increase in

147   temperature is expected to occur near 25°C (i.e., the temperature at which the slope of the

148   transmission versus temperature curve is steepest). Although some empirical support for these

149   predictions exists at broad spatial scales in the field (e.g., Wesolowski *et al.* 2015; Mordecai *et*

150   *al.* 2017; Peña-García *et al.* 2017; Caldwell *et al.* 2021), recognition of the importance of

151   nonlinear effects of temperature on transmission, especially at local scales, remains limited.

152

153   Here, we consider dengue as a case study to examine correlations between temperature

154   and disease transmission. Previous work has reported both positive and negative relationships

155   between temperature and dengue outbreaks (Caldwell *et al.* 2021). We hypothesized that

156   nonlinear effects of temperature, mediated by other climatic and non-climatic factors, might

157   explain apparent differences in the inferred effects of temperature on dengue transmission. We

158   searched the literature to test whether dengue transmission—measured as empirical

159   correlations—changes nonlinearly with average study temperature and peaks near 25°C, the

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160   temperature where the slope of the transmission versus temperature curve was suggested to be

161   greatest in a previously published trait-based mathematical model (Mordecai *et al.* 2017). We

162   also test our predictions that the strength of correlations increase positively with temperature

163   variation since it should be easier to detect effects of temperature when it is more variable, and

164   either increase or decrease with precipitation mean and variability depending on whether local

165   vector abundance is rain- or drought-driven (Lowe *et al.* 2021). Finally, we test whether

166   correlations decrease or become more negative with infection burden in the area due to depletion

167   of susceptible hosts, increase with population density due to larger epidemic potential, and either

168   decrease or become more negative with income (measured as per-capita gross domestic product;

169   GDP), which reduces outbreak potential and dampens the effects of suitable temperatures.

170

171   **METHODS**

172   **Overview**

173   To test our predictions, we synthesized published evidence of temperature–dengue

174   relationships using a systematic literature review. We compiled reported correlations between

175   temperature and dengue from previously published studies. We did not consistently have access

176   to the underlying temperature and dengue data used in the original studies that would have

177   allowed for a reanalysis of the raw data across locations. Instead, we paired each reported

178   correlation with climate reanalysis data and data on factors such as wealth and human density.

179   This means that while we did not have the underlying data used to estimate correlations in each

180   study, we did have estimates of the average temperature, average variability in temperature and

181   precipitation, population density, and other socioeconomic and climatic factors in each focal

182   study area and time period.

183

184   We used this database to answer two questions: 1) Does average study temperature

185   impact temperature–dengue relationships? and 2) How do other climatic and socioeconomic

186   factors explain variation in temperature–dengue relationships? Below, we detail the database

187   construction as well as the two separate analyses used to answer these questions.

188

189   **Database construction**

190   We downloaded abstracts and study metadata (N = 454) from Web of Science on January

191   28, 2021 (accessed through the University of British Columbia library), using the search term TS

192   = (("Aedes" OR "dengue") AND ("temperature" OR "climat*") AND ("disease*") AND

193   ("model*") AND ("incidence" or "prevalence" or "case*" or "notification*")). We then

194   systematically conducted several rounds of scoring to exclude studies with irrelevant or missing

195   information. First, we read each abstract and scored it as included or excluded based on the

196   mention of factors such as measured climatic variables and measured disease burden, incidence,

197   or prevalence. Studies were excluded if the abstract mentioned forecasting or simulations only.

198   In total, 189 of 454 abstracts were accepted. Next, we read each study with an accepted abstract,

199   and scored the study as either included or excluded based on the presence of effect sizes or

200   correlations comparing the effects of measured temperature metrics and measured disease

201   metrics. We excluded a study if only forecasting or simulation models were presented. For this

202   step, 95 of 189 papers with accepted abstracts were accepted.

203

204   We initially planned to collect data from studies that reported either a correlation between

205   temperature and dengue or a coefficient estimating the effect of temperature on dengue from a

206   regression analysis. However, our systematic literature review revealed that most of the studies

207   using regressions incorporated different covariates into their models, ranging from accounting

208   for no covariates to accounting for the effects of multiple temperature metrics, precipitation,

209   GDP, and others. We conducted simulations that illustrated how these different underlying

210   models can lead to significantly different estimates of the effects of temperature on dengue

211   despite the temperature and dengue data remaining identical across models (Supporting

212   Information), making comparisons across regression models unreliable for the purposes of our

213   study. Instead, we focused all subsequent analyses on reported correlations between temperature

214   and dengue as these models do not include any covariates, resulting in 358 reported correlations

215   from 38 studies (Table S1).

216

217   We included methodological information (hereafter referred to as study factors) for each

218   correlation, such as the location of the study, dates and length of the study, the types of

219   temperature (e.g., minimum weekly temperature, mean daily temperature) and disease metrics

220   (e.g., cases, incidence) used in the analysis, the type of correlation (Pearson, Spearman, or cross-

221   correlation), and the temporal lag of the effect of temperature. We also complemented our

222   database with data (hereafter referred to as extracted predictors) obtained from several other

223   sources. We used Google Earth Engine (Gorelick *et al.* 2017) to extract information on

224   population density and climate over the period of each study. Population density was obtained

225   from the Global Human Settlement Population Grid (JRC 2015), using the year closest to the

226   median year of each study period. Average daily mean air temperature, standard deviation in

227   daily mean air temperature, mean daily precipitation, and standard deviation in daily

228   precipitation were obtained from ERA5 (C3S 2017) and calculated over each full study period.

229   Study locations on the scale of a single city or smaller were specified using a 5 kilometer buffer

230   around point coordinates, while larger areas were mapped using shapefiles obtained from the

231   Database of Global Administrative Areas (GADM 2021). To reflect the climatic and population

232   factors most relevant to where people live (and thus where dengue cases occur), we weighted

233   these measures over space by population density. The estimated infection burden of dengue at

234   the country level (in the year 2010) was extracted from Bhatt *et al.* (2013) as a proxy for the

235   degree of population immunity or susceptibility. Country level population size in 2010 and GDP

236   per capita (adjusted for purchasing price parity in the year 2015) were obtained from the World

237   Bank (2022). Estimated dengue incidence in 2010 was calculated as estimated burden /

238   population size (see Supporting Information for more detail).

239

240   **Does average study temperature impact temperature–dengue effects?**

241   To test for a relationship across studies between mean study temperature (calculated as

242   mean average daily temperature across the study period) and observed correlation between

243   temperature and dengue within that study, we fit a series of linear mixed effects models using

244   reported correlations as response variables. Prior to fitting these models, we limited the dataset to

245   exclude observations that were generated using lags > 4 months (our estimate of the maximum

246   biologically relevant window on which temperature could directly affect dengue transmission),

247   and included only one observation per location and temperature metric per study to avoid having

248   multiple observations estimated across different lags. For example, if a study reported five

249   correlation values between minimum monthly temperature and dengue for a specific location

250   using lags of 0, 1, 2, 3, and 4 months, we would only select the observation closest to the

10

251   midpoint of 2 months. This resulted in 78 correlation observations from 37 studies (one of the 38

252   studies used only lags > 4 months).

253

254   We aimed to test whether the measured relationship between temperature and dengue

255   depended on the average temperature during the study, as well as whether ecological theory

256   based on a lab-parameterized, trait-based model of dengue transmission across temperature

257   (Mordecai *et al.* 2017) could accurately predict how correlations vary across mean temperature.

258   Specifically, we fit a null model and four alternative mixed-effects models in R (R Core Team

259   2021) using maximum likelihood with the *lmer* function (Bates *et al.* 2015). The null model

260   included only a random effect for study ID, the basic model included the study ID random effect

261   and an additional fixed effect for the type of temperature metric used in the study (minimum,

262   mean, or maximum temperature), and the final three models included the previously described

263   effects and additionally a fixed effect for either a linear effect of average temperature, a quadratic

264   effect of average temperature, or for the derivative of the transmission curve from Mordecai *et*

265   *al.* (2017) evaluated at the mean study temperature. The purpose of including this final model

266   was to compare the observed relationship based on reported correlations to the a priori

267   theoretical relationship that first motivated us to look for a concave-down pattern in correlations

268   between 20°C and 29°C. However, we note that the derivative of model-predicted dengue basic

269   reproduction number (R_0) represents a mathematical quantity that is distinct from a correlation

270   between temperature and dengue. Therefore, while we suspected that these two values may

271   follow the same qualitative patterns across temperature, they are not mathematically equivalent

272   because R_0 does not predict incidence directly (Smith *et al.* 2007).

273

274   We compared the five models using AIC (R Core Team 2021) and extracted

275   Nagelkerke's pseudo-R^2 values using the MuMIn package (Bartoń 2020). We did not incorporate

276   error around reported correlation estimates because this information was not available, though

277   we repeated the analyses described here while weighting estimates by the square root of their

278   sample size, a method used in meta-analyses when error estimates are unavailable (Hargreaves *et*

279   *al.* 2020).

280

281   **How do other climatic and socioeconomic factors explain variation in temperature–dengue**

282   **effects?**

283   Next, we aimed to test how additional climatic factors such as precipitation and

284   socioeconomic factors such as country-level GDP impacted the observed effects of temperature

285   on dengue. As described in the Introduction, we predicted that temperature–dengue correlations

286   would be more positive with higher temperature variation and population density, lower with

287   higher infection burden and GDP, and modified (either positively or negatively) by precipitation

288   mean and variability. While we originally intended to estimate how each of these extracted

289   predictors separately mediates the effects of temperature, this was not possible due to the high

290   collinearity between predictors (Fig. S2). We therefore conducted a two-step analysis, collapsing

291   the variance from all predictors with a principal component analysis (PCA) and evaluating the

292   PCA components along with study factors in linear regression models.

293

294   The PCA incorporated seven extracted predictors: log-transformed country-level GDP,

295   country-level infection incidence, and five metrics calculated by study: log-transformed

296   population density, mean precipitation, standard deviation of precipitation, standard deviation of

297   temperature, and marginal temperature suitability (the derivative of the Mordecai *et al.* [2017]

298   dengue transmission curve evaluated at the mean study temperature, as described above). We

299   sampled the unique sets of these extracted predictors, then used the *principal* function from the

300   *psych* package (Revelle 2021) to load the seven predictors across four principal components that

301   were rotated using Varimax rotation. While traditional PCA typically rotates axes to explain the

302   maximal amount of variation using the first component, Varimax rotation maximizes the sum of

303   the variances of the squared loadings, allowing for better interpretability of which predictors are

304   more strongly associated with which components.

305

306   We fit regressions using the full dataset of correlations (n=358) as response variables.

307   Predictors included the four rotated components from the PCA analysis, as well as study factors

308   to help control for variation introduced by different study methods: the temperature metric used

309   in the study (minimum, mean, or maximum), the disease metric used in the study (incidence or

310   cases), the temporal scale of the study (daily, weekly, monthly, or annual), and the type of

311   correlation used in the study (Pearson, Spearman's, or cross-correlation). We also included a

312   term for a spline (dimension of the basis = 3) for the effect of temporal lag in months on the

313   effect of temperature on dengue. We did not include interactions between these predictors. We fit

314   the regressions using the *gam* function in the *mgcv* package (Wood 2011) due to the inclusion of

315   the spline term for lags. We did not want studies that provided relatively more observations

316   (either because they estimated effects across multiple lags, multiple temperature metrics, or

317   multiple locations) to be overrepresented in our regression. We therefore bootstrapped 10,000

318   times, each time first sampling studies (n=38) with replacement and then sampling one

319   observation within that study, until we generated a dataset equal in size to the original (n=358) to

13

320   reduce overrepresentation of studies with many data points. We extracted the mean and 0.025

321   and 0.975 quantiles for each predictor coefficient estimate across the 10,000 bootstraps.

322

323   **RESULTS**

324   We obtained 358 reported correlations between temperature and dengue from 38 studies,

325   ranging from 1981 to 2017 and spanning seven global health regions (Southeast Asia, East Asia,

326   South Asia, Central Latin America, Tropical Latin America, Oceania and Caribbean; Moran *et*

327   *al.* 2012)(Fig. 1a-b). The estimates were variable with 19% negative and 81% positive (Fig. 1c).

328

329   Supporting predictions, we found that the best model included a nonlinear (quadratic)

330   effect of mean study temperature on reported correlations (ΔAIC from null model = 10.3;

331   pseudo-R^2 = 0.209). The quadratic model estimates that reported correlations peak at mean study

332   temperatures of 24.2°C (95% CI: 23.5–24.9°C; Fig. 2). The second-best model included the

333   nonlinear effect of mean study temperature calculated from the derivative of the Mordecai et al.

334   (2017) transmission curve, which peaks at 25.3°C (ΔAIC = 8.0; pseudo-R^2 = 0.165), suggesting

335   that ecological models based on vector and parasite biology can help predict how correlations

336   vary across average temperatures. The model incorporating a linear effect of mean study

337   temperature (ΔAIC = 5.0; pseudo-R^2 = 0.132) did not perform better than the basic model that

338   did not include any effect of mean study temperature (ΔAIC = 5.9; pseudo-R^2 = 0.119).

339   Repeating these analyses while weighting by the square root of the study sample size produced

340   qualitatively similar results (Supporting Information).

341

342   We then examined the factors beyond mean temperature that mediated the observed

343 relationship between temperature and dengue. Using PCA to decompose correlated climatic and

344 socioeconomic predictors into fewer, uncorrelated rotated components (RCs) meant that we were

345 not able to estimate the specific effect of each predictor on reported relationships between

346 temperature and dengue. However, this method was useful for identifying RCs that have

347 significant effects on our response, which we can then interpret as the underlying predictors

348 associated with each component having a positive or negative effect on the response.

349

350   Several RCs had a significant effect on reported correlations (Fig. 3), generally

351 supporting our hypotheses. Infection burden (RC1) had negative effects on reported correlations,

352 while temperature variation (RC1) and marginal temperature suitability (i.e., the derivative of the

353 predicted transmission curve; RC3) had positive effects. We did not have a directional prediction

354 for the effects of mean precipitation (RC2) and precipitation variation (RC2), but found that they

355 had negative effects. Higher population density was associated with two different rotated

356 components, and exhibited a significant, positive effect associated with RC1 and a non-

357 significant, positive effect when combined with lower GDP (RC4). Several study factors also

358 had significant effects on reported correlations: most notably, we found that studies that used a

359 metric of minimum or mean temperature reported more positive correlations between

360 temperature and dengue than those studies that used a metric of maximum temperature (Figs. S3-
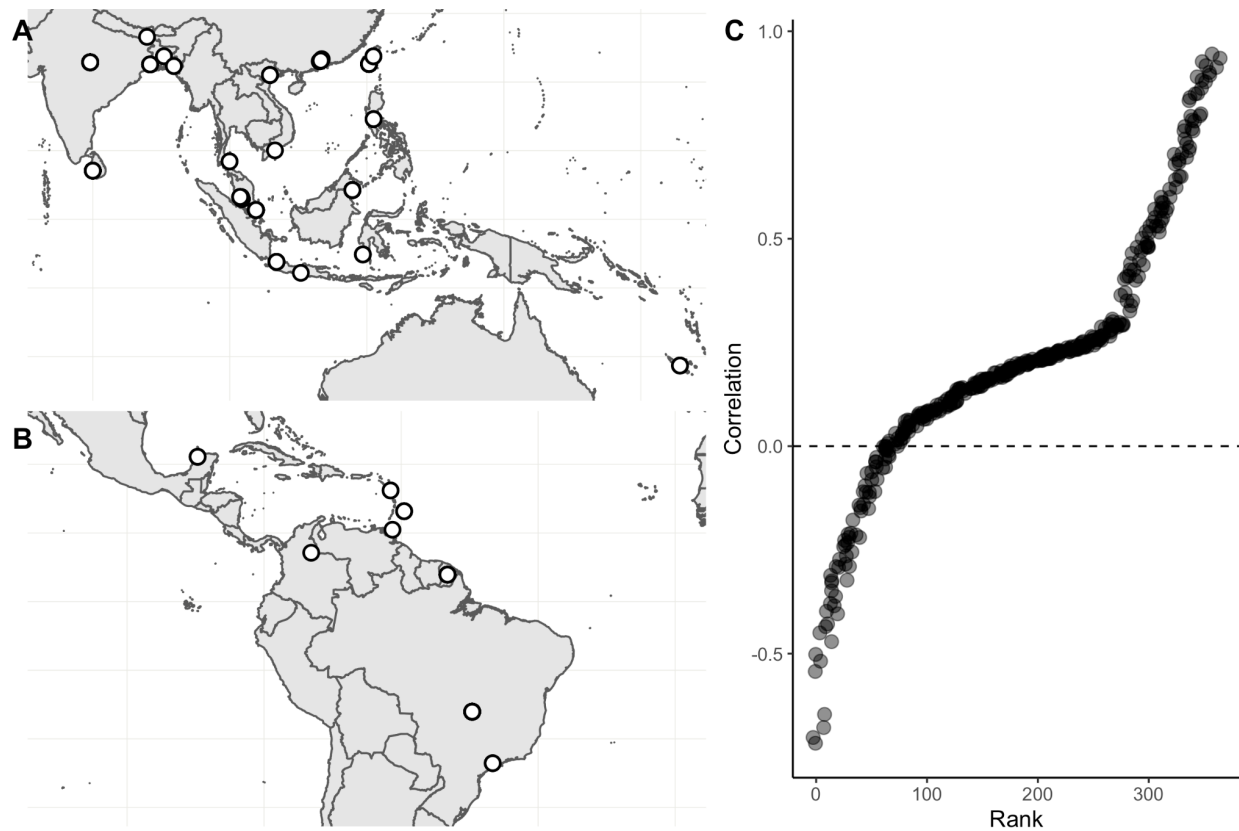
361 S4).

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Figure 1. Reported correlations between temperature and dengue range from negative to positive. a) Locations of observations in the global health regions of Southeast Asia, East Asia, South Asia, and Oceania; b) Locations of observations in the global health regions of Central Latin America, Tropical Latin America, and Caribbean; c) Jittered rank-order plot of 358 reported correlations between temperature and dengue.
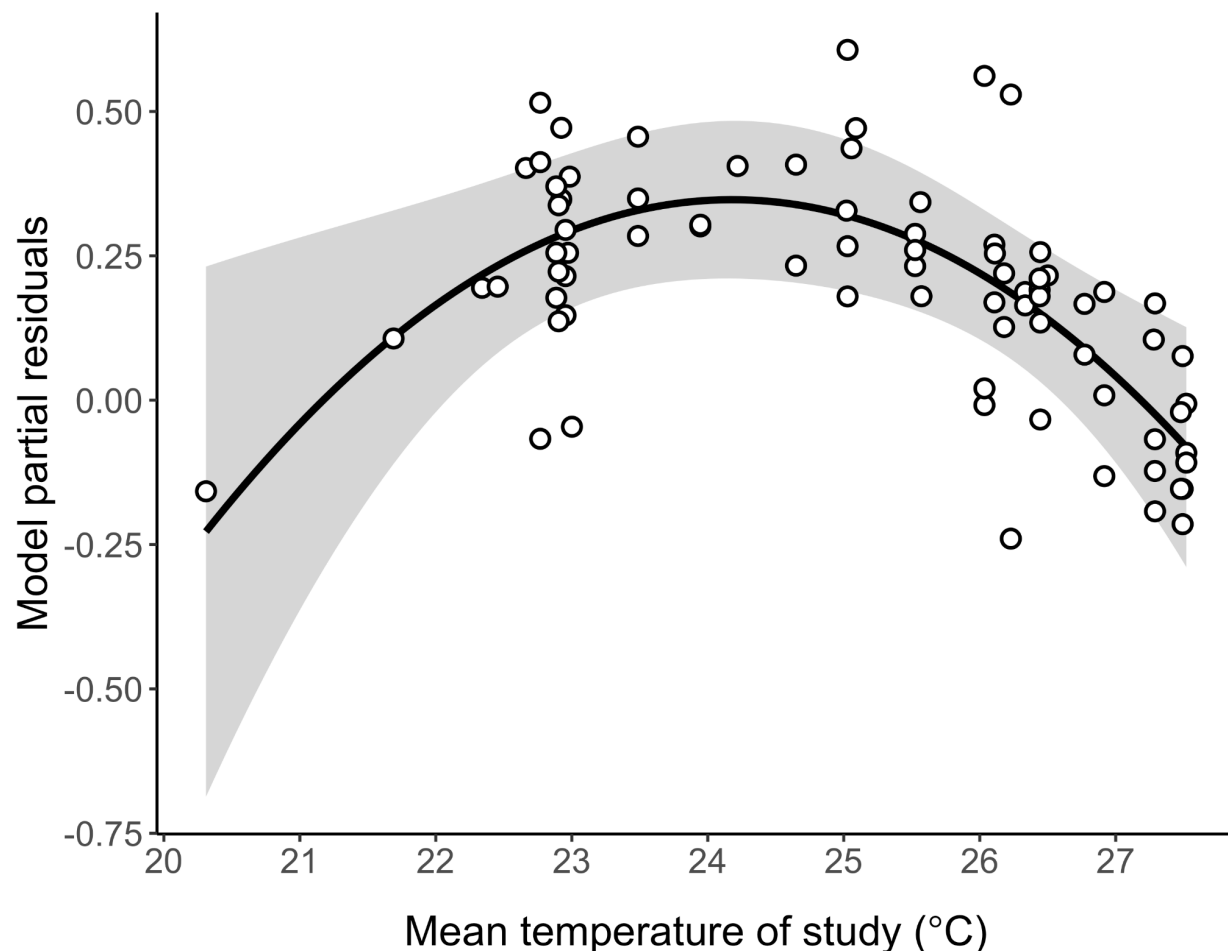
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Figure 2. Nonlinear effects of temperature on the correlation between temperature and dengue, controlling for study factors. Quadratic model partial residuals (points) and fitted predictions (black line) with 95% confidence intervals (shaded region) for the relationship between mean study temperature and reported correlations between temperature and dengue. Partial residuals and fitted predictions are from the mixed effects model with a quadratic effect of mean study temperature (black line), which was significantly better than alternative models that included a linear effect or no effect of mean study temperature (ΔAIC from null model = 10.3; pseudo-R^2 = 0.209). Partial residuals are calculated as model errors plus the model-estimated relationship between temperature and dengue. Confidence intervals generated using the *effects* package in R (Fox and Weisberg 2019). Figure S1 shows the same fitted model plotted over raw correlation data.
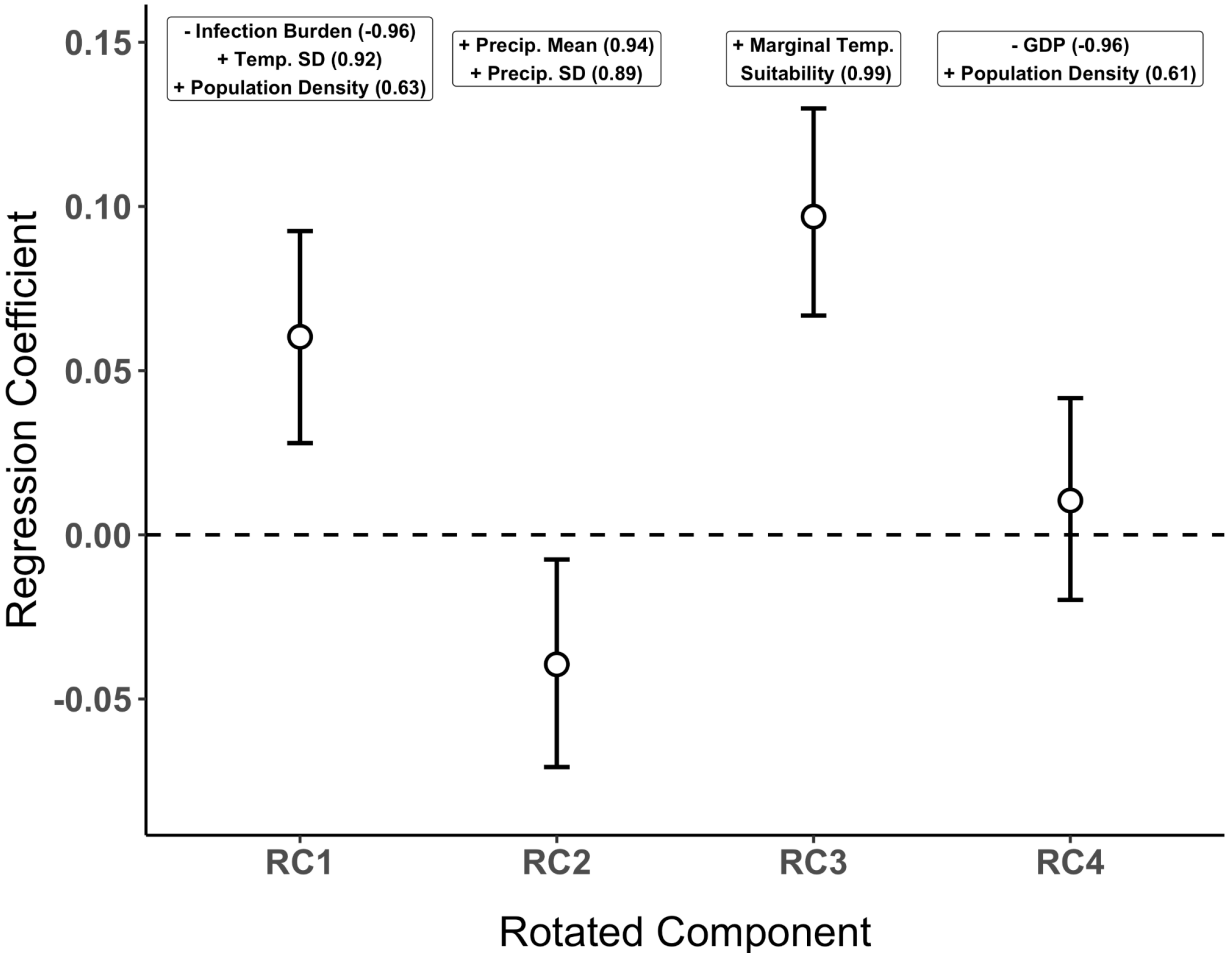
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Figure 3. Infection burden, temperature variability, population density, precipitation, and predicted temperature suitability affect the strength of temperature – dengue correlations. Mean and 95% confidence intervals of regression coefficients for four rotated components (RC) across 10,000 bootstrap runs. Annotated text above each component lists the climatic and/or socioeconomic factors most strongly associated with that component (standardized loading > |0.6|), with +/- symbols representing the sign of the association and the numbers in parentheses representing the loading (where 1 and -1 represent the strongest positive and negative associations, respectively). The sign of each association (in boxes) combined with the signs of each respective regression coefficient (points) yields the direction of the effect of each predictor on correlations (e.g., infection burden (RC1), mean precipitation (RC2) and precipitation variation (RC2) all have significant, negative effects).

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DISCUSSION

426

427   Our examination of reported correlations between temperature and dengue support

428   predictions that the effects of temperature on many ecological processes are nonlinear with small

429   or negative effects expected at low and high temperatures, and large positive effects expected in

430   some intermediate temperature range. Specifically, studies that occurred at relatively cool or

431   warm average temperatures reported lower correlations than those that occurred at temperatures

432   near the intermediate range, where transmission is expected to be most sensitive to temperature

433   (24°C). Our results illustrate that locations differ in their underlying vulnerability to warming-

434   induced disease outbreaks, and that this variability in vulnerability can be explained by

435   nonlinearity and average temperatures, as well as other climatic and socioeconomic factors such

436   as precipitation and disease burden.

437

438   The average temperature at which a study occurred had a significant quadratic

439   relationship with the correlation between temperature and dengue, with a peak at 24.2°C (95%

440   CI: 23.5–24.9°C; Fig. 2). This is close to but slightly cooler than the prediction from the

441   derivative of the trait-based, dengue transmission curve that is informed by laboratory studies on

442   the vector *Aedes aegypti* (25.3°C; Mordecai *et al.* 2017). Both the flexible quadratic temperature

443   model and the *a priori* marginal temperature suitability model (the derivative of the Mordecai et

444   al. [2017] model) were significantly better than the simpler models that assumed the correlation

445   between temperature and dengue was constant or linear across average temperature. Further, in a

446   PCA that controlled for multiple climatic and non-climatic factors, the component that was

447   highly associated with the *a priori* marginal temperature suitability model had significant

448   positive effects on correlations (Fig. 3). These results build on observations that reported

449   temperature effects on dengue varied across average temperatures or climates (Fan *et al.* 2015;

450   Li *et al.* 2020; Caldwell *et al.* 2021) by quantitatively testing whether effects vary nonlinearly as

451   predicted by ecological theory. Additionally, our database and analyses differed both by using

452   reported correlations rather than coefficients from regression models, as well as by using

453   standardized remotely sensed temperature data across studies rather than using average

454   temperatures reported by each original study. Overall, our results suggest that ecological theory

455   can be used to predict how relationships between temperature and disease vary with average

456   temperature, an often underappreciated facet of the impact of climate change on infectious

457   disease.

458

459   In addition to temperature having a direct nonlinear impact on dengue across average

460   study temperatures, we found that several other climatic factors mediated these effects. Mean

461   precipitation and variation in precipitation each had significant negative effects (via their

462   association with RC2) on reported correlations between temperature and dengue (Fig. 3).

463   Precipitation could modulate the temperature–dengue relationship through several alternative

464   mechanisms, though our approach does not allow us to differentiate between them. When

465   temperature is not strongly limiting to transmission but immature vector habitat is inconsistently

466   available, precipitation may be the main limiting factor, obscuring the relationship between

467   temperature and dengue. Alternatively, both temperature and precipitation may be limiting in

468   some settings, such that even when suitable temperatures occur there is insufficient vector habitat

469   to promote transmission. Finally, correlations between temperature and rainfall regimes (e.g.,

470   seasonality) may obscure the causal relationships between each variable and dengue. While

471   precipitation may not mediate temperature effects in all ecological or disease systems, it could

20

472   play a key mediating role in systems with animals that require pools of water for habitat or

473   breeding (e.g., other mosquito-borne diseases; Paull *et al.* 2017), in waterborne-disease systems

474   such as cholera, and in plant systems in which rainfall has been shown to impact disease levels

475   (McElrone *et al.* 2010; Eastburn *et al.* 2011).

476

477   In contrast to precipitation, average temperature variability during a study had significant

478   positive effects (via its association with RC1) on the correlation between temperature and

479   dengue, potentially because it is easier to detect correlations when temperature fluctuates over a

480   wider range. Additionally, nonlinear averaging can cause more positive effects of temperature

481   variation on dengue at ranges where the temperature–transmission relationship is concave-up

482   than concave-down (Lambrechts *et al.* 2011). Consideration of temperature variability should

483   become more important with climate change, as large changes in temperature variability and in

484   the frequency, magnitude, and duration of temperature extremes are expected in many regions

485   but their impacts on ecological processes have received relatively little attention (Easterling *et al.*

486   2000; Smith 2011; Thompson *et al.* 2013; Turner *et al.* 2020; Ma *et al.* 2021). Together these

487   results provide an important biological insight: effects of temperature on ecological processes

488   can be exacerbated or masked by other aspects of climate suitability, including rainfall and

489   variation in temperature.

490

491   Immunological and other non-climatic factors also affected local relationships between

492   temperature and dengue. As predicted, we observed a strong negative effect of infection burden

493   (as estimated for the year 2010; Bhatt *et al.* 2013), in which locations with higher levels of

494   dengue reported weaker or more negative correlations between temperature and dengue. One

21

495   possible explanation for this is that populations with historically high dengue burden have

496   proportionally high levels of immunity and partial immunity (Gubler 1998), thereby leaving

497   fewer people susceptible to infection when temperature conditions become more optimal. One

498   potential caveat when interpreting these effects is that the Bhatt *et al.* model (2013) used

499   additional data inputs beyond dengue cases—including temperature suitability—to estimate

500   country-level infection burden, meaning that estimated dengue burden is not completely

501   independent from temperature. Our predictions that population density would increase

502   temperature effects due to larger epidemic potential, while higher GDP would decrease

503   temperature effects due to higher income leading to better health infrastructure and disease

504   mitigation were generally supported (Fig. 3).

505

506   Because of the thermal physiology of organisms, we expect many ecological systems and

507   processes to be nonlinearly dependent on temperature, and these temperature effects are likely to

508   be mediated by other ecological and socioeconomic factors. Dengue provides a relatively well-

509   studied example for detecting these nonlinear and mediated effects, which may not be possible

510   for more data-limited ecological systems. Primary studies that investigate nonlinear effects of

511   temperature on ecological processes explicitly, and the mediators of these effects, are critical for

512   more generally anticipating the impact of climate change on ecological systems.

513

514   Many ecological systems are dominated by physiological processes that respond

515   nonlinearly to temperature (Brown *et al.* 2004; Dell *et al.* 2011), making them prone to climate

516   change impacts that vary in magnitude and direction across ecological settings. Recognizing this

517   nonlinearity as a fundamental driver of context-dependent responses is a critical conceptual gap

518   in many ecological studies of climate change. This can help to resolve inconsistent correlations

519   with temperature found between different field locations, as has been found with withering

520   syndrome in abalone (Ben-Horin *et al.* 2013) and sea star wasting disease (Eisenlord *et al.* 2016;

521   Menge *et al.* 2016; Harvell *et al.* 2019), as well as in other ecological contexts beyond disease

522   (Leonard 2000). At the same time, the magnitude of nonlinear effects of temperature depends on

523   a range of environmental, anthropogenic, and biogeographic factors, including climatic variation

524   in rainfall, temperature, humidity, and extreme events, human-driven changes in habitat structure

525   and species composition, and evolutionary history. Together, these factors mediate ecological

526   effects of temperature by affecting body condition, behavior, species interactions, and

527   evolutionary processes (Huey & Kingsolver 2019). Research that combines a mechanistic

528   understanding of the nonlinear impacts of temperature on ecological processes with explicit

529   consideration of important modifiers of temperature responses—through either comparative

530   approaches like that taken here or experimental approaches that manipulate multiple drivers

531   directly (e.g., Zhu *et al.* 2016)—can help to capture realistic variation in the effects of climate

532   change across settings.

533

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