Dengue Incidence and Sociodemographic Conditions in Pucallpa, Peruvian Amazon: What Role for Modification of the Dengue–Temperature Relationship?

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Abstract. Dengue is a climate-sensitive disease with an increasing global burden. Although the relationship between meteorological conditions and dengue incidence is well established, less is known about the modifying nature of sociodemographic variables on that relationship. We assess the strength and direction of sociodemographic effect modification of the temperature–dengue relationship in the second largest city of the Peruvian Amazon to identify populations that may have heightened vulnerability to dengue under varying climate conditions. We used weekly dengue counts and averaged meteorological variables to evaluate the association between disease incidence, meteorological exposures, and sociodemographic effect modifiers (gender, age, and district) in negative binomial regression models. District was included to consider geographical effect modification. We found that being a young child or elderly, being female, and living in the district of Manantay increased dengue's incidence rate ratio (IRR) as a result of 1°C increase in weekly mean temperature (IRR = 2.99, 95% CI: 1.99–4.50 for women less than 5 years old and IRR = 2.86, 95% CI: = 1.93–4.22 for women older than 65 years, both estimates valid for the rainy season). The effect of temperature on dengue depended on season, with stronger effects during rainy seasons. Sociodemographic variables can provide options for intervention to mitigate health impacts with a changing climate. Our results indicate that patterns of baseline risk between regions and sociodemographic conditions can differ substantially from trends in climate sensitivity. These results challenge the assumption that the distribution of climate change impacts will be patterned similarly to existing social gradients in health.

INTRODUCTION

Dengue epidemics have become more frequent and virulent worldwide, and emerging diseases sharing the same *Aedes* mosquito vectors—including Zika and chikungunya virus—are raising international concern regarding effective strategies for vector-borne diseases control and prevention.^{1–3} Dengue is responsible for an estimated 50–100 million cases and 10,000 death annually, and is endemic in more than 150 countries.⁴ In the absence of effective vaccination or clinical treatment, vector control and primary prevention remain the key intervention strategies. However, projected climatic changes are expected to affect local vector ecologies, making it difficult to predict the risk of spread.^{5–8} Nonetheless, it is well established that dengue incidence is affected by weather, and these relationships have been used to infer the potential for climate change to affect the distribution and/or magnitude of dengue incidence.⁹

Dengue incidence and mortality rates are affected not only by climate and weather but also by social determinants of health (such as poverty, sanitation, migration, and travel), making certain demographic subpopulations more vulnerable to infection.¹⁰ Few analyses of the drivers of dengue incidence integrate both meteorological and sociodemographic drivers, however, primarily because of methodological barriers related to combining different data types.^{11–14} An additional challenge is that the climatic and non-climatic drivers not only combine but also *interact* to affect disease outcomes.^{15,16} This implies that the extent to which weather impacts disease incidence can differ markedly across social gradients or between demographic groups.¹⁷ Social modifiers of climate impacts on

disease incidence thus provide a potentially feasible intervention alternative to alter the sensitivity of dengue incidence to weather conditions, with the potential to reduce climate change vulnerability.^{17–20} For example, although there is a well-established evidence base examining the efficacy of interventions to reduce dengue burden—insecticide-treated nets, improved health services, surveillance, and vector control—we know less about whether these interventions also modify the effect of temperature on dengue incidence.^{21–24} In the context of a changing climate, it is important to identify approaches that reduce dengue burden directly and simultaneously modify (reduce) the effect of climatic variables on incidence.

Dengue is a public health priority in the Ucayali region of Peru as it has been on the rise regionally since the early 2000s, with a major outbreak in 2012 in the capital city of Pucallpa.²⁵ The 2012 Pucallpa dengue outbreak highlights gaps in our understanding of how climatic and social determinants interact to drive disease epidemics.²⁶ With the increasing frequency of extreme weather events in the Peruvian Amazon, more research is needed on effective dengue prevention strategies based on an improved understanding of the interaction between social determinants, weather, and dengue incidence.^{27,28}

We address this gap in the literature by examining how meteorological exposures affected dengue incidence among different subpopulations—compared across different districts, genders, and ages—in Pucallpa, Peru, from 2004 to 2014. In doing so, we do not only seek to identify the determinants of dengue *incidence*—which are described elsewhere—but also seek to assess the variables that affect the *magnitude of the effect of temperature on dengue-incidence*. We aim to determine which subpopulations (defined by specific sociodemographic variables) are disproportionately affected by changes in meteorological conditions, and may

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therefore be more sensitive to future changes in climate. Our objectives are to 1) evaluate the impact of meteorological exposures on weekly dengue incidence, 2) determine how those impacts differ between dry and rainy seasons, and 3) estimate the extent to which the effect of temperature is modified by key sociodemographic variables (age, gender, and district of residence).

METHODS

Study area. Pucallpa is the second largest city of the Peruvian Amazon, with a population of about 200,000 that occupy the three districts, Yarinacocha, Manantay, and Calleria.²⁹ The city is located in the Ucayali region, south of Loreto, and shares its eastern border with Brazil. Pucallpa's population has grown rapidly, with a 3-fold increase over the last three decades, following the establishment of a road connection to the country's capital, Lima, in the 1940s.^{25,30} Rapid growth of the city created new economic opportunities in Pucallpa, particularly related to natural resources exploitation such as logging.²⁵ As a result, Pucallpa's busy commercial landscape distinguishes itself from the rest of the Ucayali region, predominantly populated by indigenous communities engaged in floodplain agriculture, fishing, hunting, and forest product gathering.^{30,31} Seasonal variations in Andean rainfall induce flooding of the Ucayali River, a formative tributary of the Amazon flowing from south to north through the Ucayali region. Flooding directly impacts livelihoods of populations living along the river, forcing many families to migrate to Pucallpa during the rainy season to look for work.³² Pucallpa is thus a highly dynamic hub in the Amazon region, and although economic prospects have evolved significantly over past decades, lack of affordable housing has resulted in a proliferation of informal settlements around the urban area, known as *asentamientos humanos*.³³ Also, there is unequal distribution of wealth across the city, as well as varying access to public infrastructure and basic urban services such as potable water and sanitation.^{29,33–36}

Outcome: dengue data. We obtained dengue records for the Ucayali region from 2004 to 2014 from the *Dirección Regional de Salud* (DIRESA) in Pucallpa. Records are completed by health practitioners at hospitals and health centers on patient visits. A confirmed dengue case is defined based on one of the following: 1) virus isolation within the first 4 days of onset of symptoms, 2) detection of the NS1 antigen, or 3) detection of IgM antibodies 5 days after the start of symptoms.^{37,38} Individual records included patient information on gender, age, residential address, diagnostic details, and date of symptoms onset. Data were stripped of personal identifiers to ensure patient confidentiality. In total, 20,082 dengue cases were reported in Ucayali between 2004 and 2014, 18,193 (91%) of which were reported in Pucallpa (districts of Calleria, Yarinacocha, and Manantay). We excluded cases with no confirmation by laboratory testing or an incomplete hospital record (missing gender, age, or district information). In total, 13,255 cases (73% of Pucallpa cases) were retained for analysis (Table 1).

Exposure: meteorological data. Daily meteorological records consisting of maximum, mean, and minimum temperatures, as well as cumulative rainfall, were obtained from the *Servicio Nacional de Meteorología e Hidrología del Perú* for the years 2004–2014. Two climate stations (Las Palmeras Ucayali

TABLE 1
Reported number of dengue cases in Pucallpa for the study period (2004–2014), Dirección Regional de Salud

Data description	Number of cases (% total)
Total number of cases reported in Pucallpa	18,193 (100)
Laboratory-confirmed cases	15,814 (87)
Laboratory-confirmed cases with information on locality	13,259 (73)
With complete records (for address, age, and gender)	13,255 (73)

and Aguaytia) were selected based on proximity to Pucallpa and completeness of the climate data record for the study period. Daily meteorological records were aggregated by week. We generated time lags up to 12 weeks for all meteorological records⁹ and identified the lag for which each variable was most strongly associated (highest coefficient in unconditional univariable negative binomial regression) with weekly dengue counts. Incorporating a time lag into our meteorological exposures allowed us to account for the expected delay between change in weather conditions and dengue cases, as a result of environmental and biological processes. We retained mean weekly temperature at a 4-week lag as our key meteorological independent variable for analysis based on four considerations: 1) published empirical evidence on the validity of mean temperature as a biologically plausible driver of vector abundance and disease transmission,^{39–41} 2) evidence of high collinearity (Spearman's coefficient $\geq |0.6|$) between minimum, mean, and maximum temperature variables, 3) mean temperature had the strongest bivariate association with weekly dengue cases in our dataset, and 4) our a priori focus on effect modification rather than specification of a detailed model of meteorological exposures associated with incidence.

Effect modifiers: sociodemographic data. Weekly dengue counts were stratified based on gender, age, and district. Age was categorized into the following groups: young children (< 5 years), children and adolescents (5–17 years), adults (18–64 years), and elderly (≥ 65 years). We hypothesize that age and gender may modify the relationship between temperature and dengue infection because these individual characteristics often predict certain roles and behavior (and ultimately time spent in proximity to mosquito-breeding sites), and therefore impact one's exposure to the infection. We used district ($n = 3$) to evaluate whether the effect of weather on dengue incidence was uniform across different geographical units or not. We limited extrapolating conclusions to socioeconomic effect modification using the district-level data because although some differences can be observed between districts in census data, resolution was too coarse to account for individual variations, and, most importantly, the census information was cross-sectional and did not allow for a longitudinal analysis. Pucallpa is situated in three districts: Calleria, Yarinacocha, and Manantay.

Data analysis. We used a negative binomial multivariable regression model with total weekly dengue cases for Pucallpa as our dependent (outcome) variable. We selected the binomial model after comparing its goodness of fit with other regression models, namely, the Poisson, the zero-inflated Poisson, and the zero-inflated negative binomial models. We evaluated model robustness using the Vuong test, Bayesian information criteria (BIC) values, and by comparing predicted

and actual probabilities (using the countfit command in Stata). We used yearly, stratum-specific population estimates (for every age category, gender, and district combinations) as the exposure (offset) variable for our statistical analyses. Population data were obtained through the Instituto Nacional de Estadística e Informática (INEI)'s online census database.^{42,43}

We first ran a baseline (no interaction) model with socio-demographic and meteorological exposures, and then incorporated interactions to evaluate effect modification among variables. We also tested for different combinations of sociodemographic and meteorological exposures to evaluate whether associations varied based on the inclusion/exclusion of specific variables. We ran the model for the entire study period (2004–2014) and for the outbreak year only (2012) to compare estimates from both scenarios. We included interaction terms between weekly mean temperature and the following variables: age, gender, district, and season. The associations between the interaction terms and the outcome are an indicator of effect modification (interaction) of the temperature–dengue relationship by age, gender, and/or district.

We included a number of covariates in the model. The number of days with any rain (by week), with a lag of 11 weeks, was included as a control because it was not collinear with mean temperature and had a strong association with the dengue outcome based on bivariable tests (that association was stronger than the association with other related meteorological variables such as weekly sum and average of precipitations). We retained season in the final model to account for interaction between mean temperature and season. We tested for collinearity and made sure to not include covariates that were highly correlated (Spearman coefficient $\geq |0.6|$). We also incorporated a categorical variable for time periods (2004–2006, 2007–2010, and 2011–2014) to account for interannual variability in dengue incidence. This allowed us to account for interannual changes in control and surveillance, and for the substantial increase in dengue incidence that took place during a 2012 outbreak in Pucallpa. Table 2 lists the

variables included in our model for analysis and Figure 1 below provides a causal model framework to help clarify the expected role of each variable in the statistical model we used.

To illustrate the size, direction, and confidence interval of interactions, we plot marginal effects for each interacting variable as well as linear combinations of estimates for all possible combinations of season, district, gender, and age. We included all control and interaction variables in a single model to account for confounding between variables. The BIC was used to assess whether hypothesized interaction variables (reflecting effect modification) contributed to model fit. The Huber–White robust standard errors estimation provided a variance estimate adjusting for temporal autocorrelation (clustering at the weekly level). We ran sensitivity analyses including (2004–2014) and excluding data from the year 2012 to test for unique patterns during and outside of the 2012 outbreak. All analyses were conducted in Microsoft Excel v.2013 (Microsoft Corp., Redmond, WA) and STATA v.13 (Stata Corp., College Station, TX).

The final model equation used for analyses was the following:

$$\begin{aligned} \ln(\text{weekly dengue counts}) &= \beta_0 + \beta_1(\text{mean weekly temperature L4}) + \beta_2(\text{season}) \\ &+ \beta_3(\text{sex}) + \beta_4(\text{age}) + \beta_5(\text{district}) + \beta_6(\text{year periods}) \\ &+ \beta_7(\text{number of days with any rain by week}) \\ &+ \beta_8(\text{mean weekly temperature L4} \times \text{season}) \\ &+ \beta_9(\text{mean weekly temperature L4} \times \text{sex}) \\ &+ \beta_{10}(\text{mean weekly temperature L4} \times \text{district}) \\ &+ \beta_{11}(\text{mean weekly temperature L4} \times \text{age}) \\ &+ \ln(\text{population}), \end{aligned}$$

where $\ln(\text{weekly dengue counts})$ is the outcome of the negative binomial regression (natural logarithm of weekly dengue counts); β_0 is the intercept and β_{1-11} are coefficients; L4 refers to a lag of 4 weeks; and $\ln(\text{population})$ is the population offset.

TABLE 2
Description of variables used in regression analysis

Variables used in regression analyses	Description
Dependent (outcome) variable	
Weekly dengue cases in Pucallpa	Counts
Independent (exposure) variable	
Mean weekly temperature (4-week lag)	Continuous (°C)
Sociodemographic variables (effect modifiers)	
Gender	Dummy variable: 0 = male and 1 = female
Age (years)	Categorical variable: Ref: < 5, 5–19, 20–64, and > 65
District	Categorical variable: Ref: Manantay, Yarinacocha, and Calleria
Interaction terms used to test for effect modification	
Interaction variable: season $\times$ mean weekly temperature (lagged 4 weeks)	Product of season and mean weekly temperature (lagged 4 weeks)
Interaction variable: gender $\times$ mean weekly temperature (lagged 4 weeks)	Product of gender and mean weekly temperature (lagged 4 weeks)
Interaction variable: district $\times$ mean weekly temperature (lagged 4 weeks)	Product of district and mean weekly temperature (lagged 4 weeks)
Interaction variable: age $\times$ mean weekly temperature (lagged 4 weeks)	Product of age and mean weekly temperature (lagged 4 weeks)
Covariates	
Number of days with any rain, by week (lagged 11 weeks)	Continuous (number of days)
Season	Dummy variable: Ref: dry season (May–October) and rainy season (November–April)
Year periods	Categorical variable: Ref: 2004–2006, 2007–2010, and 2011–2014
Population exposure (offset) variable	
Yearly population estimates, strata-specific	Continuous (number of people)

FIGURE 1. Causal model framework.

Ethics. Ethics approval for this research was received by the McGill University Research Ethics Board and is consistent with the Canadian Tri-Council's requirements for the Ethical Conduct of Research Involving Human Subjects. Access to, and use of, dengue surveillance data was approved by DIRESA Ucayali.

RESULTS

Descriptive statistics. Dengue incidence was consistently higher during the rainy season (November–April) throughout

the study period (2004–2014). Figure 2 shows seasonal trends in dengue cases. The 2012 dengue outbreak also occurred during the rainy season, as a result of proximal and distal causes discussed in Charette et al.²⁶ The average age of patients with dengue in Pucallpa during the study period was 23.9 years old (95% CI: 23.5–24.1) and 52% of all cases were female patients. The mean average weekly temperature (lagged 4 weeks) was 25.2°C in the dry season compared with 26.2°C in the rainy season. Total weekly precipitation during the rainy season (mean: 124.7 mm) was close to three times of

FIGURE 2. Dengue cases and meteorological exposures in Pucallpa, 2004–2014. (A) Monthly averaged mean weekly temperature. (B) Monthly averaged weekly number of days with any rain. This figure appears in color at www.ajtmh.org.

TABLE 3

Meteorological and sociodemographic factors associated with dengue incidence in Pucallpa, comparing models with and without interactions between temperature and the following: gender, age, season, and district

Variables	Model without interactions IRR (95% CI)	Model with interactions (effect of 1°C increase on mean temperature on dengue) IRR (95% CI)
	That is, what is the (estimated) effect of this variable on dengue incidence?	That is, what is the (estimated) effect of temperature on dengue incidence assuming interactions with gender, age, season, and district variables
Average weekly temperature (lag 4 weeks)	1.43 (1.18–1.75)	–
Gender (ref. male)		
Female	1.04 (0.98–1.11)	1.64 (1.12–2.40)
Age (years) (ref. less than 5 years old)		
5–19	1.43 (1.27–1.61)	1.08 (0.78–1.50)
20–64	1.31 (1.16–1.48)	0.93 (0.70–1.23)
65 and older	0.85 (0.73–0.98)	1.49 (1.03–2.15)
Season (ref. dry season)		
Rainy season	5.32 (3.31–8.57)	2.07 (1.51–2.82)
District (ref. Manantay)		
Calleria	1.52 (1.36–1.71)	0.73 (0.61–0.86)
Yarinacocha	1.06 (0.90–1.25)	0.71 (0.58–0.86)

IRR = incidence rate ratio.

that in the dry season (mean: 56.1 mm). The average number of days with any rain per week was 3.3 during the dry season and 3.8 during the rainy season. More dengue cases were reported in the rainy season (weekly mean: 41.2, 95% CI: 23.8–58.6) compared with the dry season (weekly mean: 5.1, 95% CI: 2.4–7.9). Strata-specific incidence rates were calculated using mid-period (2009) baseline population data.† Incidence rates were generally higher for men and women less than 19 years old, in all districts. Incidence rates were mostly higher for women than for men (see Supplemental Table 1). Overall, incidence rates were lowest in Yarinacocha.

Baseline model (without interaction/effect modification).

Increasing average weekly temperature (lag 4 weeks) and occurrence of rainy season were associated with increases in dengue incidence rates (Table 3, model without interactions). Gender was not associated with dengue incidence in our baseline model. Between the years 2004 and 2014, the district of Calleria had a dengue incidence rate 1.52 times greater (95% CI: 1.36–1.71) than that of Manantay. There was no difference in the incidence rate between populations from Yarinacocha compared with Manantay. Compared with young children (less than 5 years old), the age category with the largest difference in dengue incidence was children/adolescents (5–19 years old), with an incidence rate ratio (IRR) of 1.43 (95% CI: 1.27–1.61). The effect sizes for season, precipitation, and temperature were larger—with the same directionality—during the 2012 outbreak than their effects for the study period as a whole (for the model with 2012 data only, see Supplemental Table 2).

Evidence of effect modification in the temperature–dengue relationship. The impact of temperature on dengue incidence differed between men and women, across age-groups and districts, and between the rainy and dry seasons, as indicated by interaction terms in the final model (Table 3, Figure 3). Figure 3 suggests a nonlinear relationship between temperature increase and change in IRR, which limits our interpretation of +1°C change in mean weekly temperature, but we chose to avoid over-specifying our model and focus on the interpretability of the effect modification. The increase in

dengue incidence associated with a +1°C change in mean weekly temperature ranged from nil to 2.86, and was greater in the rainy than in the dry season (Table 4, Figure 4). This trend held true for all strata (all categories of age, gender, and districts). The strongest effect modification was between the rainy and dry seasons. The effect of temperature on dengue was greatest during the rainy season in the district of Manantay and lowest among individuals aged 5–64 years during the dry season in Calleria (the wealthiest district) and Yarinacocha. Analyses restricted to 2012 (outbreak year), or excluding 2012, did not differ meaningfully from the results using data from the full study period.

The effect of temperature on dengue incidence differed between genders. The IRR—reflecting the effect of temperature on dengue—was higher among females than males, and this pattern was consistent across all ages and districts (Table 4, Figure 4). However, confidence intervals overlapped in all strata, offering limited support for gender as a modifier for the dengue–temperature relationship.

A one-degree increase in weekly mean temperature had a greater impact on dengue incidence among young children (< 5 years) and older adults (> 65 years) than in the middle age-groups (youth and adults). This pattern was consistent across seasons, genders, and districts. There was limited overlap of confidence intervals of IRRs for young children/older adults with IRRs for youth/adults, suggesting a large effect size for age, this effect being even greater in the rainy season (Figures 3 and 4).

Differences were found in the effect of temperature on dengue incidence between districts, and these patterns differed from those observed in the model without interaction terms. Despite higher dengue incidence rates in Calleria, dengue incidence was most sensitive to temperature change in the district of Manantay (Table 4). Effect sizes in Calleria were similar to those in Yarinacocha but were substantially higher in Manantay. Although effect sizes during the dry season were modest in Calleria and Yarinacocha, they were much larger even in population strata with the smallest effects in Manantay. Taking, for example, women aged between 5 and 19 years, the following IRRs were reported in the different districts: Calleria IRR = 1.14, 95% CI: 0.82–1.59, Yarinacocha IRR = 1.11, 95% CI: 0.8–1.54, and Manantay IRR = 2.08, 95%

† Incidence rate = $\frac{\text{Number of new cases in district } \times}{2009 \text{ population district } \times 11 \text{ years}} \times 1000$

FIGURE 3. Marginal effects of (A) season, (B) age, (C) district, and (D) gender on the temperature–dengue relationship in Pucallpa, with 95% CIs. (A) Marginal effects of season interaction on the predicted number of dengue cases per week for increasing average weekly temperature, lag 4 weeks. (B) Marginal effects of age interaction on the predicted number of dengue cases per week for increasing average weekly temperature, lag 4 weeks. (C) Marginal effects of district interaction on the predicted number of dengue cases per week for increasing average weekly temperature, lag 4 weeks. (D) Marginal effects of gender interaction on the predicted number of dengue cases per week for increasing average weekly temperature, lag 4 weeks. This figure appears in color at www.ajtmh.org.

CI: 1.53–2.84. The effect of temperature on dengue incidence was highest among children < 5 years and the elderly (> 65 years) during the rainy season in Manantay, with effect sizes nearing 3.0 (IRR range: 2.72–2.99 among these strata). Overall, effect sizes in Manantay were 35–30% higher than in Calleria or Yarinacocha across all strata and seasons.

DISCUSSION

We sought to assess the extent to which age, gender, and district acted as modifiers for the effects of weather on dengue incidence in an endemic region of Peru. By examining dengue surveillance data and meteorological conditions from

TABLE 4

Dengue incidence rate ratios (IRRs) for 1°C increase in weekly mean temperature derived using a linear combination of estimates (table version of the plotted estimates in Figure 3).

Sex	Age	Calleria				Yarinacocha				Manantay			
		Dry season		Rainy season		Dry season		Rainy season		Dry season		Rainy season	
		IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Female	< 5	1.63	1.12–2.4	2.16	1.57–2.99	1.60	1.09–2.33	2.12	1.51–2.97	2.25	1.4–3.63	2.99	1.99–4.5
Male	< 5	1.56	1.08–2.25	2.07	1.51–2.82	1.52	1.05–2.19	2.02	1.45–2.8	2.15	1.35–3.41	2.85	1.92–4.23
Female	5–19	1.14	0.82–1.59	1.51	1.16–1.97	1.11	0.8–1.54	1.47	1.11–1.96	1.57	1.06–2.33	2.08	1.53–2.84
Male	5–9	1.08	0.78–1.5	1.44	1.11–1.87	1.06	0.77–1.46	1.40	1.06–1.86	1.49	1.02–2.19	1.98	1.47–2.68
Female	20–64	0.97	0.73–1.3	1.29	0.99–1.68	0.95	0.72–1.26	1.26	0.95–1.68	1.34	0.96–1.87	1.78	1.34–2.36
Male	20–64	0.93	0.7–1.23	1.23	0.94–1.61	0.90	0.69–1.19	1.20	0.9–1.6	1.28	0.93–1.76	1.70	1.29–2.23
Female	> 65	1.56	1.07–2.28	2.07	1.49–2.88	1.52	1.06–2.2	2.02	1.44–2.83	2.15	1.37–3.38	2.86	1.93–4.22
Male	> 65	1.48	1.03–2.15	1.97	1.43–2.73	1.45	1.01–2.07	1.92	1.38–2.69	2.05	1.32–3.18	2.72	1.86–3.97

IRR = incidence rate ratio.

FIGURE 4. Dengue incidence rate ratios for a 1°C increase in average weekly temperature by season, gender, district, and age, for the entire study period (2004–2014) derived using linear combinations of estimates, with 95% CIs. (A) Calleria, dry season. (B) Calleria, rainy season. (C) Yarinacocha, dry season. (D) Yarinacocha, rainy season. (E) Manantay, dry season. (F) Manantay, rainy season.

Pucallpa over a 10-year period, we found mixed results that both confirm and challenge current understanding of dengue–climate risk relationship.

Overall, our results corroborate findings that highlight an association between increasing temperature and higher dengue incidence.^{40,44–48} There are numerous identified causal pathways including the expansion of vector range and population density, enhanced blood digestion and thus biting rate of the vector *Aedes aegypti*, and reduced extrinsic incubation period of the virus within the vector.^{39–41} We found that increasing temperature had a greater impact on dengue incidence during the rainy season compared with the dry season. Seasonality of dengue is recognized throughout endemic zones to drive fluctuations in infection rates and partially determine the timing of outbreaks.^{49–52} In our dataset, the number of days with any rain was negatively associated with dengue incidence in Pucallpa, with decreasing dengue rate per unit (day) increase. By contrast, total weekly precipitation was not strongly associated with dengue incidence. The rainy season, however, was associated with higher

dengue incidence rates and was identified as a modifier of the temperature–dengue relationship, reflecting the complex association between rainfall and dengue risk. During the dry season, potential breeding sites dry out more quickly than in the rainy season, whereas abundant rains in the wet season can flush away larvae from stagnant waters.^{53,54}

Importantly, our results indicate that projections of climate risk based on meteorological proxies cannot reliably predict impacts on dengue based on temperature changes alone, because these effects will be mediated by concurrent changes in precipitation. Increased temperatures under dry conditions, for example, would have lower impact than increased temperatures combined with sufficient rainfall. Notably, these variables should not simply be combined within climate projections, but rather should be allowed to interact within models, reflecting the importance of seasonality as an effect modifier of the temperature–dengue relationship. Our assessment of effect modification with a 1-degree increase in weekly average temperature may limit our study's conclusions to specific climate change scenarios reflecting trends and

conditions specific to the study period. Given potential unpredictable weather changes that may occur in the Peruvian Amazon as a result of broader climate change, our analysis may not directly align with the actual changes.^{27,28}

Age is often described as a determinant for dengue morbidity and mortality, and this is intrinsically linked to immunological status and the presence of comorbidities in an individual.^{10,55} Our results show that age was a modifier of the temperature–dengue relationship, with an increase in mean temperature more strongly affecting dengue incidence in young children (aged < 5 years) and older adults (aged > 65 years). Young children are not always reported as having higher incidence rates than older groups, but many studies suggest that they are more vulnerable to dengue, which could be a consequence of their higher microvascular permeability.^{56,57} Other studies have shown that older age-groups are more likely than children to have clinical dengue, as sometimes first infection is asymptomatic.^{58–61} Although high rates of dengue infection and illness have been documented in young children and elderly, our results do not directly provide evidence that these groups are at heightened risk of infection (from our baseline model without interactions), but that they show a disproportionate increase in risk with increasing temperatures and meteorological suitability for vector breeding. Additional pathways through which age might modify the vulnerability of certain groups to increase in temperature could be related to behavior, for example, young children spending more time indoors during warmer weather or in close proximity to mosquito-breeding environments.

We hypothesized that gender may modify the temperature–dengue relationship in a similar manner to age, in particular because of gender roles affecting time spent exposed to *Ae. aegypti*–breeding environments. We found that although dengue risk increased more rapidly with temperature change among women compared with men, the effect size was small, with overlapping confidence intervals. Research exploring gender and gender differences in dengue risk and infection has found that gender alone cannot explain higher risk of dengue infection, as the male:female ratio of incidence often varies by age.^{59,62,63} Researchers generally suggest that occupation and culturally prescribed gender roles (and ultimately time spent at home) have an impact on a subject's exposure to the infection because the vector is most active during daylight hours, and around domestic environments.^{59,61,64} Despite reports of higher rates of dengue among men in the rural Amazonia,⁶⁵ other studies in Peru have detected higher rates of infection in women than men.^{66–68} Our results indicate that women may experience a greater impact—albeit from lower baseline risk—on dengue incidence because of increasing temperatures, particularly during the rainy season. Gender differences are small, however, suggesting that gender may not be a critical driver of dengue infection in a changing climate, or that occupational/livelihood risks may not clearly differentiate by gender and gender roles.

We investigated whether district of residence was an effect modifier of the dengue–temperature relationship, inquiring whether temperature had a varying effect on dengue incidence based on geography. Our results indicate that not only did effects vary between districts—confirming evidence of effect modification by district—but also that the patterning of these effects differed from those seen in the model without interactions. The baseline model of dengue incidence

indicated that dengue rates were higher in Calleria than in Manantay or Yarinacocha, with the latter two showing similar incidence. Calleria is Pucallpa's largest and most populated district, but has much lower population density than Yarinacocha and Manantay. According to the census data available when the study took place, Calleria has lower levels of poverty, illiteracy, and percent of the population malnourished, and a small population proportion lacking access to a sewage system and running water in the home, than the districts of Manantay and Yarinacocha. Calleria is a district with overall lower poverty and prevalence of child malnutrition than the two other districts. Yarinacocha and Manantay have comparable socioeconomic and sociodemographic characteristics, which further limits our analysis of socioeconomic effect modifier using district as unit of reference. Despite highest overall incidence rates in Calleria, dengue incidence was most sensitive to changes in temperature in the district of Manantay. As such, the population in Manantay may be more vulnerable to increases in mean temperature than those in Calleria and Yarinacocha, particularly during the rainy season. There was, however, little variation in IRRs between Calleria and Yarinacocha. Indeed, the baseline risk and effect modification profiles of the three districts differed considerably, with Manantay showing lower overall risk but high sensitivity to temperature, Calleria showing high overall risk and moderate sensitivity to temperature, and Yarinacocha showing lower overall risk and modest sensitivity to temperature. These risk profiles were not clearly aligned with—or explicable by—the census information describing sociodemographic and socioeconomic characteristics of each district, indicating that other factors may contribute to the varying risk profiles and/or that district may not be an appropriate scale to evaluate socioeconomic trends (Table 5).

Our results are consistent with mixed results reported in the literature regarding the role of poverty in driving dengue incidence.^{19,63} Studies aiming to assess the dengue–poverty relationship use a variety of proxies for wealth, ranging from income, asset-based indices, and access to public services to education.^{65,69–71} This wide range of proxies and scales reduces the comparability and possibility for consensus among studies examining poverty as a risk factor or effect modifier for dengue.¹⁹ The association between dengue incidence and poverty depends also on the connection between the poverty proxy used and vector-breeding environment. Environments with standing water (clean or not) in artificial containers are ideal breeding sites for the dengue vector.⁷² In some contexts, poorer neighborhoods or households might host more of these sites, and in others not. In Pucallpa, all districts use water tanks to store water. In addition, the presence of artificial containers and use of larvicide vary in the city as do garbage collection services, educational opportunities, environmental behavior and purchasing power to buy items, and receptacles for water. Thus, it is possible that we may not have detected vulnerabilities to a temperature increase among certain districts because the variable district does not adequately reflect predisposing factors for optimal mosquito-breeding environment in Pucallpa.

Despite these complexities, the differing district risk profiles may reflect a number of pathways through which increase in temperature impacts dengue incidence. For example, the window of time during which people are exposed to mosquitoes might be patterned differently as temperature increases

TABLE 5
Socioeconomic and sociodemographic indicators by district, Pucallpa

Socioeconomic and sociodemographic indicators	Pucallpa districts		
	Calleria	Manantay	Yarinacocha
Population 2007 (latest census year)	136,478	70,745	85,605
Area (km ²)	10,278	660	198
Population density (n/km ²)	13	107	433
Population in poverty (%)	14.9	22.5	26.2
Population in extreme poverty (%)	1.8	2.3	3.6
Chronic malnutrition in children (< 5 years old) (%)	19.5	27.8	24.3
Illiteracy among population > 15 years old (%)	1.6	2.3	2.2
Households without running water in the home (%)	38.9	55.7	63.2
Households without sewage system (%)	44.7	81	69.3
Households without access to street lighting (%)	19.9	34.1	29.5
Population with health insurance (%)	39.8	36.8	44.7

Sources data: refs. 29,42,43, and 73.

in the separate districts. Access to air conditioning, quality of home infrastructure, and type and level of employment can affect urban people's exposure to *Ae. aegypti*-breeding sites (mostly around the home) as temperature increases. Our observation of higher dengue rates in the "wealthier" district (Calleria) may also reflect higher reporting due to greater access to health care and education.²⁹ Ucayali's regional hospital is located within the Calleria district, so this may lead to more people reporting to the hospital.⁷³ To account for the possibility of patients from other districts reporting in Calleria, we ensured that the district we used for analyses was the patient's home district and not that of the hospital. Additional reasons why dengue rates are overall greater in Calleria may have to do with higher vector densities from greater number of containers available as breeding sites, greater inflow of diseased individuals, or even greater boat and car traffic in general.^{25,74} Also, sewage facilities at the household and municipality level are least developed in Manantay, making residents dependent on the river for disposal of all types of waste.⁷³ Fewer sewage facilities in Manantay may mean reduced breeding sites for *Ae. aegypti*, and partially explain lower baseline dengue rates in comparison with Calleria.⁷⁵ These remain as hypotheses, however, that would require further investigation to be confirmed as possible mechanisms for higher dengue rates in Calleria. Based on our analysis, we can only confirm that geography does have an impact the dengue-temperature relationship in Pucallpa, although we cannot infer what aspect of the district characteristics may explain some of these variations.

Our study has key limitations inherent to the nature of our data. Relying on hospital records as a proxy for total dengue incidence in Pucallpa means that only reported cases could be included in our analysis; thus, our data are prone to a selection bias. Given different health-care seeking behavior and access based on gender, age, and socioeconomic conditions, some groups of individuals might be underrepresented/overrepresented in our analysis. Underreporting from lower socioeconomic areas, for example, because of limited access to health units, would result in our underestimation of the moderating impact of low socioeconomic status (SES) on dengue incidence. A proxy for SES that provides more variation, at a finer geographic scale, such as measures of sanitation, poverty index, or other proxies for breeding environment or health service access, would be required to investigate whether these results could be replicated with improved variation in SES measures. We did not have

access to neighborhood-level socioeconomic or detailed environmental data within Pucallpa. Additional control variables would have considerably enhanced our analysis, including ethnicity, more detailed information on SES, livelihoods, family size, and exact neighborhood location within Pucallpa.

Our findings address a gap in the vulnerability literature by examining the influence of sociodemographic variables on temperature-related morbidity.¹⁸ Although few studies look at effect modification of SES on the climate-health relationship, these variables are the ones that are most amenable to intervention—compared with weather or climate, for example. Our study adds to the evidence of modifying effects by age on vulnerability to dengue incidence resulting from an increase in mean temperature, and provides early signals for the potential role of geography and gender. Our results provide tentative support—and a methodological framework—for theories positing a role for social gradients in modifying climate impacts on health, as well as highlighting the role of geographical (district in this case) context in determining an individual's vulnerability to disease through social disadvantage.⁷⁶

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