1 2	The Impact of Temperature and Precipitation on All-Infectious-, Bacterial-, and Viral- Diarrheal Disease in Taiwan
3 4	Gerry Andhikaputra ¹ , Amir Sapkota, PhD ² , Yu-Kai Lin, PhD ³ , Ta-Chien Chan, PhD ^{4,5} , Chuansi Gao, PhD ⁶ , Li-Wen Deng ¹ , Yu-Chun Wang, PhD ^{1,7}
5 6	^{1*} Department of Environmental Engineering, College of Engineering, Chung Yuan Christian University, 200 Chung-Pei Road, Zhongli 320, Taiwan
7 8	² Department of Epidemiology and Biostatistics, University of Maryland School of Public Health
9 10	³ Department of Health and Welfare, University of Taipei College of City Management, 101 Zhongcheng Road Sec. 2, Taipei 111, Taiwan
11 12	⁴ Research Center for Humanities and Social Sciences, Academia Sinica, 128 Academia Road, Section 2, Taipei, Taiwan
13 14	⁵ Division of Ergonomics and Aerosol Technology, Faculty of Engineering, Lund University, Lund 223 62, Sweden
15 16	⁶ Institute of Public Health, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
17 18	 ⁷ Research Center for Environmental Changes, Academia Sinica, 128 Academia Road, Section 2, Nankang, Taipei 11529, Taiwan
19	Address correspondence and reprint requests to:
20	*Yu-Chun Wang, PhD
21	Professor
22	Chung Yuan Christian University College of Engineering
23	200 Chung-Pei Road
24	Zhongli 320, Taiwan
25	Telephone: 886-3-265-4916; Fax: 886-3-265-4949
26 27	E-mail: ycwang@cycu.edu.tw; swingapple@gmail.com
28	Keywords: infectious diarrhea; extreme weather; climate change; dlnm
29 30	Number of words: 300 in abstract and 2834 in text. This manuscript has 1 table, 3 figures, 51 references, and supplementary 2 tables and 4 figures

31 **ABSTRACT**

32 Background: The ongoing climate change will elevate the incidence of diarrheal in 2030-2050 in Asia, including Taiwan. This study investigated associations between 33 meteorological factors (temperature, precipitation) and burden of age-cause-specific 34 35 diarrheal diseases in six regions of Taiwan using 13 years of (2004-2016) population-based 36 data. 37 Methods: Weekly cause-specific diarrheal and meteorological data were obtained from 38 2004 to 2016. We used distributed lag non-linear model to assess age (under five, all age) 39 and cause-specific (viral, bacterial) diarrheal disease burden associated with extreme high (95th percentile) and low (5th percentile) of climate variables up to lag 8 weeks in six 40 regions of Taiwan. Random-effects meta-analysis was used to pool these region-specific 41 estimates. 42 Results: Extreme low temperature (<5th percentile) was associated with risks of all-43 infectious and viral diarrhea, with the highest risk for all-infectious diarrheal found at lag 44 8 weeks among all population [Relative Risk (RR): 1.44; 95% Confidence Interval (95% CI): 45 46 1.24–1.67]. The highest risk of viral diarrheal infection was observed at lag 2 weeks regardless the age. Extreme high temperature was associated with risk of bacterial 47 diarrheal among all-age (RR: 1.07; 95% CI: 1.02-1.13) at lag 8 weeks. Likewise, extreme 48 49 high precipitation was associated with all infectious diarrheal, with the highest risk 50 observed for bacterial diarrheal among population under five years (RR: 2.77; 95% CI:

- 1.60–4.79) at lag 8 weeks. Extreme low precipitation was associated with viral diarrheal
- in all-age population at lag 1 week (RR: 1.08; 95% CI: 1.01–1.15)].
- Conclusion: In Taiwan, extreme low temperature is associated with an increased burden
- of viral diarrheal, while extreme high temperature and precipitation elevated burden of
- 55 bacterial diarrheal. This distinction in cause-specific (viral vs. bacterial) and climate-
- 56 hazard specific (extreme low vs. extreme high temperature, precipitation) diarrheal
- 57 disease burden underscore the importance of incorporating differences in public health
- 58 preparedness measures designed to enhance community resilience against climate
- 59 change.

INTRODUCTION

61

62

63

64

65

66

67

68

69

70

71

72

73

74

75

76

77

78

79

80

81

82

With over 1.6 million annual deaths, children under five accounted for more than half a million, the diarrheal disease continues to be a major killer globally in 2016 [1]. Infectious diarrhea is still a common disease in children in Taiwan, despite the rotavirus vaccine implementation in the country [2, 3]. While low-income countries bear a disproportionate burden of diarrheal disease, acute infectious diarrheal is also known to be a significant contributor to morbidity in high-income countries [4]. The major etiological agents for diarrheal disease include bacteria, viruses, and parasites [5]. In Taiwan, infectious diarrheal diseases, i.e., cholera, typhoid/ paratyphoid fever, bacillary dysentery, amoebic dysentery, and enterohemorrhagic E. coli infection are classified as notifiable diseases as per the provisions of the Taiwan Communicable Disease Control Act [6, 7]. Other infectious diarrheal diseases (norovirus, rotavirus, non-typhoidal Salmonella, non-toxigenic Vibrio cholerae, Staphylococcus aureus, Cactus bacilli, and Vibrio parahaemolyticus) are not part of notifiable diseases; however, prior studies have shown that they can create diarrheal disease outbreak in Taiwan and are a threat to population health [8].

Prior studies have identified several risk factors related to diarrheal diseases, including young age, male gender, young maternal age, lack of maternal education, early weaning, and low practice of water, sanitation, and hygiene (WASH) [9, 10]. Others have suggested that diarrheal disease transmission depends on favorable climatic conditions [11, 12], which may explain seasonal patterns in transmission [10]. A recent Taiwan study reported more than 4,500 disability-adjusted life years (DALYs) were attributable to

foodborne illnesses resulting from non-typhoid *Salmonella*, Norovirus, and Vibrio *parahaemolyticus* [13]. Bacterial diarrheal peaks in summer season (July) with lower incidence during winter season [14], whereas viral diarrheal, particularly caused by rotavirus, commonly happens during the dry and cold months in Taiwan [14-16].

The latest IPCC (AR6) report projected climate changed related increases in heavy rain and temperature [17], which may elevate burden of diarrheal disease in the Asian subcontinent. Previous study from Nepal showed a 4.40% and 0.28% increase diarrheal disease incidence with a 1°C increase in mean temperature (RR: 4.40%; 95% CI: 3.95–4.85) and 1 cm increase in rainfall (RR: 0.28%; 95% CI: 0.15–0.41), respectively [12]. Likewise, a combined study from Taiwan, Hong Kong, and Japan showed 21% increases in diarrheal disease risk during the cold month (RR: 1.22; 95% CI: 1.08–1.36) [18].

The most recent IPCC report suggests that despite mitigation effort, extreme event frequency will continue to rise in the foreseeable future because of the changes that have already taken place [17]. It is critical to develop public health adaptation strategies against climate change threats. With regards to diarrheal disease, such adaptation measures require a better understanding of the underlying population's vulnerability to the specific causative agents (bacterial, viral, and parasite) and climate hazard (extreme heat, cold, extreme precipitation, drought). While a number of studies have linked extreme weather variables (temperature and precipitation) with burden of diarrheal disease [18, 19], there is a paucity of data at a national level and the latest year in Taiwan. Hence, this study aims to investigate the temperature- and precipitation-related infectious disease risks of all-infectious, bacterial, and viral diarrheal in six regions

of Taiwan (i.e., North, Chumiao, Central, Yunchianan, Kaoping, and Huatung region) for all-age and under-five years' population using 13 years (2004-2016) national health insurance data.

MATERIALS AND METHODS

Study area

Taiwan, a subtropical island (150 km x 350 km) with 23.5 million people [20, 21], is located in one of the main paths of the western North Pacific Ocean's tropical cyclone that has been experiencing drastic impacts of climate change. This study focused on six regions in Taiwan, including North, Chumiao, Central, Yunchianan, Kaoping, and Huatung regions, as study areas (Supplementary Figure S1).

Data sources

We collected weekly cause-specific diarrheal disease data (2004-2016) for cities of Taiwan from reimbursement records of the outpatient visit of the National Health Insurance (NHI) database from the Ministry of Health and Welfare. NHI provides equal access to health care in Taiwan and covers more than 99% of Taiwan's population [22]. The data was retrieved as an aggregate count and all identification number of insured population were randomized into surrogate numbers for users, thus, the patient privacy is protected. Before we do the analysis we summarized the weekly city-level data into region-level data. This study used the 9th and 10th Revision of the International Classification of Diseases codes (ICD-9) and (ICD-10) to identify diarrheal disease cases. These included bacterial cases [V. cholera, Salmonella spp., E. coli, campylobacter enteritis, Yersinia enterocolitica, Clostridium difficile, and other bacteria (ICD-9: 001, 003, 008 and

ICD-10: A00, A02, A04)], virus cases [Rotavirus, Adenovirus, and Norwalk virus (ICD-9: 8.61-63 and ICD-10: A08.0, A08.2, A08.1)], and all other infectious diarrheal cases [ICD-9: 001-009 and ICD-10: A00-09]. The study was approved by the institutional review board (IRB) at the Chung Yuan Christian University, Taiwan, and the University of Maryland, United States.

We retrieved weather data from the Taiwan Central Weather Bureau, including average temperature (°C), precipitation (mm), sunshine hour (hour), and relative humidity (%) for 18 weather stations located in six regions of Taiwan for the same period. Weather data was aggregated from hourly resolution to weekly resolution for the analysis to match the temporal resolution of the outcome measures.

The population data for each region, stratified by age group, was extracted from National Statistics, Republic of China (R.O.C) that provides open access to the yearly population. Further detailed information about population data is available on their official portal (https://eng.stat.gov.tw/).

Non-linear association between weekly weather variables and cause-specific diarrheal risks

This study evaluated the effects of weekly average temperature and cumulative precipitation on Taiwan's age-cause-specific infectious diarrheal using distributed lag non-linear model (DLNM) proposed by *Gasparrini et al.* [23]. DLNM has been used to assess the relationship between weather variables and infectious diseases in epidemiological studies [24, 25]. In this study, we used Poisson regression specified as:

Log[Y]~BS(T,lag) + BS(Precipitation, lag) + NS(SH, 4) + NS(RH, 4) + NS(time, 7 * year) + Lunar New Year holiday

Where Y is the age-cause-region-specific weekly cases of outpatient visits, and T is the region-specific weekly average temperature. We set temperature-diarrheal risk association as the basis spline (BS) function with five degrees of freedom (*df*). Weekly regional cumulative precipitation was also set as the BS function with five *df*. We analyzed the lag effect from 0 to 8 weeks. The sunshine hours (SH) and relative humidity (RH) were included in the analysis as cofounder and were set as the natural splines (NS) with 4 df. The variable "time" was included to control long-term trends and seasonal effects [26]. We also included Lunar New Year holiday as a covariate in the model as this is known to be associated with diarrheal disease burden in Taiwan [27].

The effects of extreme low and high were reported at the 5th and 99th percentile of weekly average temperature and weekly average cumulative precipitation. We decided to use same optimum values throughout all the lag weeks by averaging the results of lag 2 weeks because it has more significant risks in comparison to other lag values. We tested several model combinations, which simultaneously included extreme temperature and precipitation variable, and selected a model based on lower Akaike information criterion (AIC).

We used random effect meta-analysis to combine region-specific relative risk (RR) of age and cause-specific diarrheal associated with weekly extreme temperature and extreme precipitation. We computed all analyses using the *mgcv*, *dlnm*, and *mvmeta* package in R (version 3.3.3).

RESULTS

A total of over ten million diarrheal disease cases were reported from 2004 to 2016 in Taiwan (**Table 1**). The weekly average cases was 2,266 for all infectious diarrheal, 71 for bacterial diarrheal, and 5 for viral diarrheal. The weekly trends of cause-specific diarrheal case per 100,000 population by age from 2004 to 2016 are illustrated in **Figure 1**. An upward trend was observed for all infectious diarrheal cases, while bacterial diarrheal cases showed downward trends. Viral diarrheal cases were higher during 2006-2012, with a more stable rate observed from 2013-2016. The weekly average temperature during the study period was 23.53°C across the six regions of Taiwan, with 36.20 mm precipitation, 5.16 hour of sunshine, and relative humidity of 76.86% (Table 1). The temporal trends of weekly average temperature, precipitation, sunshine hour, and relative humidity are depicted in **Supplementary Figure S2**.

Figure 2 depicts the pooled RRs of age and cause-specific diarrheal associated with weekly average temperature in Taiwan from 2004 to 2016 for each lag period (Lag 0 to 8 weeks). The optimum value of temperature was set as 25°C. The optimum value was identified based on average value at lag of 2 weeks as a declining risk was seen afterwads (Figure 2). Further analysis showed that the risk of all infectious diarrheal was significant at extreme low temperature (15.30 °C) for all-age group after 2 weeks (lag 2) and for under-five years after 5 weeks (lag 5) (Supplementary Table S1). The risks were persistent up to 8 weeks lag among all studied group with the highest risks observed for lag 8, with RR of 1.44 (95% CI: 1.24–1.67) and 1.42 (95% CI: 1.25–1.61) for all age and under-five years population, respectively. We also found a positive association between extreme low

temperature and viral diarrheal with the highest risk at lag 2, regardless of age. The highest risk was 1.41 (95% CI: 1.24–1.60) for all age and 1.22 (95% CI: 1.08–1.39) for under-five years population.

The results of this study did not indicate any significant effect of extreme low temperature on bacterial diarrheal at all lag. However, extreme high temperature (31.07°C) was associated with increases in bacterial diarrheal among all-age population at lag 8 (RR: 1.07; 95% CI: 1.02–1.13). We found that the risk of viral diarrheal vanished after lag 3 weeks, and viral diarrheal was not associated with extreme high temperature.

The results of extreme temperature for the pooled analyses were similar with the region-specific analyses. **Supplementary Figure S3** shows that population was more vulnerable to all-infectious diarrheal and viral diarrheal at lower temperatures than the high temperatures. In contrast, bacterial diarrheal risks was elevated at higher temperature in Taiwan. Low temperature significantly increased the risks of all infectious diarrheal at lags 0-2 in regions of North and Chumiao, but after lag of 2 weeks among the study population in regions of Yunchianan and Kaoping. Meanwhile, the effects of high temperature appeared on all infectious diarrheal among study groups after 6 weeks in Taiwan, except for Kaoping and Huatung.

We observed positive association between extreme high precipitation and all infectious diarrheal disease after 1 week lag for under-five age group, with the highest risk observed at lag 3 (RR:1.15; 95% CI: 1.05–1.27) (**Supplementary Table 2**). Meanwhile, the effects of extreme high precipitation showed up after lag 2 weeks among all-age

population, with the highest RR of 1.15 (95% CI: 1.03–1.28) was observed at lag 4 (**Figure 3**). All-age population and population aged 0-5 years were at the highest risk of bacterial diarrheal after exposure of extreme high precipitation, RR is 1.47 (95% CI: 1.07–2.03) at lag 7 weeks and 2.77 (95% CI: 1.60–4.79) at lag 8 weeks, respectively. We also observed higher viral diarrheal burden associated with extreme precipitation among the younger age group at lag 2 (RR: 1.76; 95% CI: 1.05–2.93). In addition, viral diarrheal infection was positively associated with extreme low precipitation (0 mm) in all-age population 1.08 (95% CI: 1.01–1.15) at lag 1 week.

The relative risk of age-, area-, cause-, and lag-specific diarrheal associated with weekly cumulative precipitation in six regions of Taiwan can be seen in **Supplementary Figure S4**. The effects of high precipitation on all infectious diarrheal was apparent after lag 1 week in all regions of Taiwan. Meanwhile, the effects of high precipitation on bacterial and viral diarrheal only appeared after lag 1 week in regions of North, Chumiao, Central, and Yunchianan.

DISCUSSION

Climate change driven increases in frequency of extreme weather events and their projected trend in the near future, irrespective of mitigation efforts, have highlighted the societal need for enhanced public health adaptation strategies. Using 13 years of surveillance data, we quantified the impact of extreme temperature and precipitation events on the burden of bacterial and viral diarrheal in Taiwan. Our data suggest that extreme low temperature increases risk viral diarrheal while extreme high temperature

increases risk of bacterial diarrheal in all-age population. In our study, extreme high precipitation was clearly associated with all cause-specific diarrheal in Taiwan while extreme low precipitation was associated with the risk of viral diarrheal among all-age population.

Our findings are in agreement with previous studies that have linked bacterial diarrheal with extreme heat events, while the risk of all-infectious diarrheal and viral diarrheal were found to be associated with extreme low temperature [28-30]. A recent study from Taiwan reported a cluster of diarrheal infection caused by rotavirus during the cooler months [31]. Likewise, prior studies have reported that lower temperature promotes rotavirus and norovirus infections [32-35]. For viral infection that is conveyed through fomite contamination or droplet, the favorable environment is a main factor of infectivity [36]. On the contrary, bacterial diarrheal agents such as *Salmonella* and *Campylobacter* thrive in hotter temperatures [37]. Others have reported higher temperature can increase the risk of infectious diarrheal, potentially due to increase in consumption of uncooked meat or spoiled food [38-41].

Similar to a recent multinational study that reported the association between temperature and acute diarrheal to persist up to 7 weeks [18]. The increases in risks of all-infectious diarrheal associated with extreme heat in our study lasted up to lag of 8 weeks and extreme cold related viral diarrheal persistent up to lag of 3 weeks. The prolonged effects of all-infectious diarrheal might be caused by re-infected cases and lack of effectiveness of the treatment [42]. Similar to our finding, a Chinese study reported that the risk of viral diarrheal is affected by low temperature within one week [43]. Moe

et al reported that rotaviruses work better in terms of replication and survival in cold temperature (4 °C or 20 °C) despite the relative humidity [44], which could enable them to persist on contaminated surfaces. On the contrary, the less apparent effect of extreme high temperature on diarrheal might be explained because the population in Taiwan is more adapted to sweltering summer [18].

Taiwan is highly vulnerable to various environmental hazards, including high seismic activity, monsoons, and typhoons [45]. Typhoons in Taiwan are known to worsen surface water quality, which may increase the burden of diarrheal disease [8]. Increases in water turbidity and pathogen loads due to natural hazards resulting in drinking water contamination may explain some of the observed increases in risk [46, 47]. Taiwan Water Resources Agency reported a steady increment in daily domestic water consumption per person, starting with 268 L in 2012, 274 L in 2014, and 275 L in 2016 [48]. A recent Taiwanese study linked torrential rainfall with a higher risk of bacillary dysentery and enteroviruses infections [49], similar to studies from other parts of the world [50, 51]. We observed a significant association between extreme high precipitation and cause-specific diarrheal with a noted exception for viral diarrheal among all age population.

The one-week lag we observed between extreme precipitation and diarrheal disease may be related to the incubation period of the pathogens. A previous study from Taiwan reported an incubation period ranging from 2-10 days for enteroviruses and bacillary dysentery, which agrees with our results [19]. Others have reported acute gastrointestinal symptoms to persist up to one month after the extreme precipitation event [47]. This finding along with our observation of elevated diarrheal disease risk up

transmission. A report from Taiwan CDC indicated that viral gastroenteritis clusters are likely to happen in school areas, including elementary, middle, and high schools, followed by restaurant areas and campsite [52]. Younger populations tend to wash their hands less frequently [53] which may lead to higher chance of transmission among students.

This present study has several strengths, including long temporal coverage (2004–2016) of weekly cause-specific diarrheal at the national level. Our exposure metric consisted of extreme events derived using thresholds that were specific to location and time of year, and as such highly relevant in the context of climate change. In addition, high-quality hospitalization data enabled us to perform separate analyses for bacterial and viral diarrheal as well as age-stratified analysis. There are noted limitations as well. For instance, we did not have individual-level data regarding medication use, rotavirus vaccination status, and income level. Likewise, the personal information that may modify the risk of cause-specific diarrheal, including the presence of a refrigerator, and dietary intake before the symptom onset were not available.

Conclusion

We investigated extreme heat- and extreme precipitation-related risk of morbidity of all-infectious, bacterial, and viral diarrhea among Taiwanese population. Evidence suggested that all population regardless of age are at elevated risk of all-infectious and viral diarrheal during exposure of extreme low temperature. While, the risk of extreme high temperature only appeared in bacterial diarrheal among all-age population. Moreover, the extreme high precipitation was significantly affected the risk of cause-specific diarrheal in Taiwan. In addition, we observed higher risk of viral diarrheal among all-age population during the extreme low precipitation. Our data points to underlying heterogeneity in risk that is associated with specific climate hazards (extreme cold vs extreme heat, extreme precipitation vs drought) as well as pathogens (bacterial vs viral diarrheal). Public health adaptation strategies need to account for such differences for it to have a meaningful impact.

Acknowledgement: We would like to thank the Ministry of Health and Welfare, Environmental Protection Administration (EPA) and Central Weather Bureau, Executive Yuan for providing research data. We also would like to thank The Ministry of Science and Technology, Taiwan (MOST) and National Science Foundation for providing the support and funding. These Interpretations and conclusions herein do not represent the views of these agencies. The views or opinions expressed in this article are those of the writers and should not be construed as opinions of the Taiwan EPA and MOST. Mention of trade names, vendor names, or commercial products does not constitute endorsement or recommendation by Taiwan EPA and MOST.

Financial Support: This study was supported by grants from the Taiwan Ministry of Science and Technology (MOST 108-2625-M-033-002-; MOST 109-2625-M-033-002-; MOST 110-2625-M-033-002-). Additional support was obtained from the US National Science Foundation (NSF) through Belmont Forum (Award Number (FAIN): 2025470).

Conflict of Interest: None

- **Ethics approval and consent to participate:** All methods were carried out in accordance with relevant guidelines and all protocols were approved by Taiwan National Health Research Institutes (code: EC1090703-F-E).
- Availability of Data and Materials: Data not available due to [ethical/legal/commercial]
 restrictions.
- Author contributions and consent for publication: G.A., A.S. and Y.C.W Conceptualization;
 Y.C.W, G.A., and Y.K.L. Writing Original Draft; L.W.D. and Y.C.W Formal analysis; and

- Y.C.W, A.S., C.T.C, C.G, and G.A. Writing Review & Editing. All authors read and approved
- the final version of the manuscript for the publication.

- 1. Collaborators, G.B.D.D.D., Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. Infectious diseases, 2018. **18**(11): p. 1211-1228.
- Lu, M.-C., et al., The impact of rotavirus vaccination in the prevalence of gastroenteritis
 and comorbidities among children after suboptimal rotavirus vaccines implementation in
 Taiwan: A population-based study. Medicine, 2021. 100(25): p. e25925.
- 3. Lin, F.-J., et al., *Clinical and epidemiological features in hospitalized young children with*341 *acute gastroenteritis in Taiwan: A multicentered surveillance through 2014–2017.*342 Journal of the Formosan Medical Association, 2022. **121**(2): p. 519-528.
- Collaborators, G., GBD Diarrhoeal Diseases Collaborators Estimates of global, regional,
 and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic
 analysis for the Global Burden of Disease Study 2015. Lancet Infect Dis, 2017. 17: p. 909 948.
- Chang, H., et al., *Aetiology of acute diarrhoea in children in Shanghai*, *2015–2018*. PLOS
 ONE, 2021. **16**(4): p. e0249888.
- 349 6. Ministry of Health and Welfare Communicable Disease Control Act. 2019.
- Yang, H. Development of Laws and Regulations on Communicable Diseases Control in
 Taiwan. 2000.
- 352 8. Lin, F.-H., et al., *An Increased Risk of School-Aged Children with Viral Infection among Diarrhea Clusters in Taiwan during 2011–2019*. Children, 2021. **8**(9): p. 807.
- Mokomane, M., et al., The global problem of childhood diarrhoeal diseases: emerging
 strategies in prevention and management. Therapeutic advances in infectious disease,
 2018. 5(1): p. 29-43.
- 357 10. George, C.M., et al., *Risk factors for diarrhea in children under five years of age residing*358 *in peri-urban communities in Cochabamba, Bolivia.* The American journal of tropical
 359 medicine and hygiene, 2014. **91**(6): p. 1190-1196.
- Rieckmann, A., et al., Exploring Droughts and Floods and Their Association with Cholera
 Outbreaks in Sub-Saharan Africa: A Register-Based Ecological Study from 1990 to 2010.
 Am J Trop Med Hyg, 2018. 98(5): p. 1269-1274.
- Dhimal, M., et al., Effects of Climatic Factors on Diarrheal Diseases among Children
 below 5 Years of Age at National and Subnational Levels in Nepal: An Ecological Study.
 Int J Environ Res Public Health, 2022. 19(10).
- 13. Lai, Y.-H., et al., *Disease burden from foodborne illnesses in Taiwan, 2012–2015.* Journal of the Formosan Medical Association, 2020. **119**(9): p. 1372-1381.
- Chung, N., et al., Clinical and epidemiological characteristics in hospitalized young
 children with acute gastroenteritis in southern Taiwan: According to major pathogens. J
 Microbiol Immunol Infect, 2017. 50(6): p. 915-922.
- Yang, S.Y., et al., Epidemiology and clinical peculiarities of norovirus and rotavirus
 infection in hospitalized young children with acute diarrhea in Taiwan, 2009. J Microbiol
 Immunol Infect, 2010. 43(6): p. 506-14.
- Lu, T.M., et al., Gastroenteroviruses infection in Taiwan. Open Infectious Diseases
 Journal, 2009. 3(1): p. 37-43.

- 17. IPCC, W., Climate change 2022: impacts, adaptation and vulnerability. Contribution of
 Working Group II to the Fourth Assessment Report of the Intergovernmental Panel on
 Climate Change. Cambridge University Press, Cambridge, UK, 2022.
- 379 18. Chen, C.-C., et al., *The Association between Ambient Temperature and Acute Diarrhea* 380 *Incidence in Hong Kong, Taiwan, and Japan.* Sustainability, 2018. **10**(5): p. 1417.
- 381 19. Chen, M.-J., et al., *Effects of Extreme Precipitation to the Distribution of Infectious* 382 *Diseases in Taiwan, 1994–2008.* PLOS ONE, 2012. **7**(6): p. e34651.
- Dept. of Household Registration, M.o.t.I.R.o.C.T. *Statistics*. 2020 [cited 2021 15] February]; Available from: https://www.ris.gov.tw/app/en/3910.
- Lee, S. and D. Tseng, *Review and perspective of expressway tunnels in Taiwan, China.*Journal of Rock Mechanics and Geotechnical Engineering, 2011. **3**: p. 385-397.
- 387 22. Hsieh, F.I. and H.Y. Chiou, *Stroke: morbidity, risk factors, and care in taiwan.* J Stroke, 388 2014. **16**(2): p. 59-64.
- 389 23. Gasparrini, A., B. Armstrong, and M.G. Kenward, *Distributed lag non-linear models*. Stat 390 Med, 2010. **29**(21): p. 2224-34.
- 391 24. Yi, L., et al., The impact of climate variability on infectious disease transmission in China:
 392 Current knowledge and further directions. Environ Res, 2019. 173: p. 255-261.
- 25. Lowe, R., et al., Nonlinear and delayed impacts of climate on dengue risk in Barbados: A modelling study. PLoS Med, 2018. **15**(7): p. e1002613.
- Kim, H., et al., Alternative adjustment for seasonality and long-term time-trend in time-series analysis for long-term environmental exposures and disease counts. BMC Medical
 Research Methodology, 2021. 21(1): p. 2.
- Taiwan Centers for Disease Control. *This year's viral gastroenteritis activity highest in 4*years; As long weekend approaches, public urged to pay attention to personal hygiene to
 ensure their health and health of others. 2015 [cited 2022 February]; Available from:
 https://www.cdc.gov.tw/En/Bulletin/Detail/82YfTeXRr1MgY9WyDPMi7A?typeid=158.
- 402 28. Eze, J.I., et al., *The association of weather and bathing water quality on the incidence of*403 *gastrointestinal illness in the west of Scotland*. Epidemiology and infection, 2014. **142**(6):
 404 p. 1289-1299.
- Carlton, E.J., et al., *A systematic review and meta-analysis of ambient temperature and diarrhoeal diseases.* International Journal of Epidemiology, 2015. **45**(1): p. 117-130.
- 407 30. Ghazani, M., et al., *Temperature Variability and Gastrointestinal Infections: A Review of Impacts and Future Perspectives.* International journal of environmental research and public health, 2018. **15**(4): p. 766.
- 410 31. Lee, W.-T., et al., *Salmonella/rotavirus coinfection in hospitalized children*. The Kaohsiung Journal of Medical Sciences, 2012. **28**(11): p. 595-600.
- 412 32. Parashar, U.D., E.A.S. Nelson, and G. Kang, *Diagnosis, management, and prevention of rotavirus gastroenteritis in children.* BMC 2018.
- 414 33. Lestari, F.B., et al., *Rotavirus infection in children in Southeast Asia 2008-2018: disease*415 *burden, genotype distribution, seasonality, and vaccination.* J Biomed Sci, 2020. **27**(1): p.
 416 66.
- 417 34. Chiejina M and S. H., *Viral Diarrhea*, in *In: StatPearls [Internet]*. [Updated 2020 Nov 19]: 418 Treasure Island (FL): StatPearls Publishing.
- 419 35. Mertens, A., et al., Associations between High Temperature, Heavy Rainfall, and
 420 Diarrhea among Young Children in Rural Tamil Nadu, India: A Prospective Cohort Study.
 421 Environ Health Perspect, 2019. 127(4): p. 47004.

- 422 36. Lopman, B., et al., Host, Weather and Virological Factors Drive Norovirus Epidemiology:
 423 Time-Series Analysis of Laboratory Surveillance Data in England and Wales. PLOS ONE,
 424 2009. 4(8): p. e6671.
- 425 37. Hall, G.V., et al., *The influence of weather on community gastroenteritis in Australia.*426 Epidemiology and Infection, 2011. **139**(6): p. 927-936.
- 427 38. Zhou, X., et al., *High temperature as a risk factor for infectious diarrhea in Shanghai,* 428 *China.* Journal of epidemiology, 2013. **23**(6): p. 418-423.
- 39. Ziska, L., et al., Ch. 7: Food Safety, Nutrition, and Distribution, in The Impacts of Climate
 430 Change on Human Health in the United States: A Scientific Assessment. 2016, U.S. Global
 431 Change Research Program: Washington, DC. p. 189–216.
- 432 40. Jiang, C., et al., *Climate change, extreme events and increased risk of salmonellosis in Maryland, USA: Evidence for coastal vulnerability.* Environ Int, 2015. **83**: p. 58-62.
- 434 41. Morgado, M.E., et al., Climate change, extreme events, and increased risk of
 435 salmonellosis: foodborne diseases active surveillance network (FoodNet), 2004-2014.
 436 Environ Health, 2021. 20(1): p. 105.
- 437 42. Hao, Y., et al., Effects of ambient temperature on bacillary dysentery: A multi-city
 438 analysis in Anhui Province, China. Science of The Total Environment, 2019. **671**: p. 1206439 1213.
- 440 43. Lu, W., et al., Short-Term Impacts of Meteorology, Air Pollution, and Internet Search
 441 Data on Viral Diarrhea Infection among Children in Jilin Province, China. International
 442 journal of environmental research and public health, 2021. **18**(21): p. 11615.
- 443 44. Moe, K. and J.A. Shirley, *The effects of relative humidity and temperature on the survival of human rotavirus in faeces.* Archives of Virology, 1982. **72**(3): p. 179-186.
- 445 45. Kuo, Y.-C., M.-A. Lee, and M.-M. Lu, *Association of Taiwan's Rainfall Patterns with Large-*446 *Scale Oceanic and Atmospheric Phenomena*. Advances in Meteorology, 2016. **2016**: p.
 447 3102895.
- 448 46. Galway, L.P., et al., Hydroclimatic variables and acute gastro-intestinal illness in British
 449 Columbia, Canada: A time series analysis. Water Resources Research, 2015. 51(2): p.
 450 885-895.
- 47. Chhetri, B.K., et al., Associations between extreme precipitation and acute gastrointestinal illness due to cryptosporidiosis and giardiasis in an urban Canadian drinking water system (1997–2009). Journal of Water and Health, 2017. **15**(6): p. 898-907.
- 454 48. Taiwan Water Resources Agency, Statistics of domestic water consumption.
- 45. Chen, M.J., et al., Effects of extreme precipitation to the distribution of infectious diseases in Taiwan, 1994-2008. PLoS One, 2012. **7**(6): p. e34651.
- 457 50. Checkley, W., et al., *Effect of El Niño and ambient temperature on hospital admissions* 458 for diarrhoeal diseases in Peruvian children. Lancet, 2000. **355**(9202): p. 442-50.
- 459 51. Mukabutera, A., et al., *Rainfall variation and child health: effect of rainfall on diarrhea*460 *among under 5 children in Rwanda, 2010.* BMC Public Health, 2016. **16**(1): p. 731.
- Wu, F.-T., Surveillance of viral diarrheal outbreaks and developing the rapid screening
 methods. 2014, Taiwan Centers for Disease Control.
- van Beeck, A.H.E., et al., Children's hand hygiene behaviour and available facilities: an observational study in Dutch day care centres. European Journal of Public Health, 2015.
 26(2): p. 297-300.

- 1 Figures Legend
- 2 Figure 1. Weekly trend of cause-specific diarrhea stratified by sex and age in Taiwan
- 3 from 2004 to 2016
- 4 Figure 2. Pooled relative risks of age-cause-lag-specific diarrhea associated with weekly
- 5 average temperature in Taiwan from 2004 to 2016 (Purple= all age; Yellow= under 5
- 6 years)
- 7 Figure 3. Pooled relative risks of age-cause-lag-specific diarrhea associated with weekly
- 8 cumulative precipitation in Taiwan from 2004 to 2016 (Purple= all age; Yellow= under 5
- 9 years

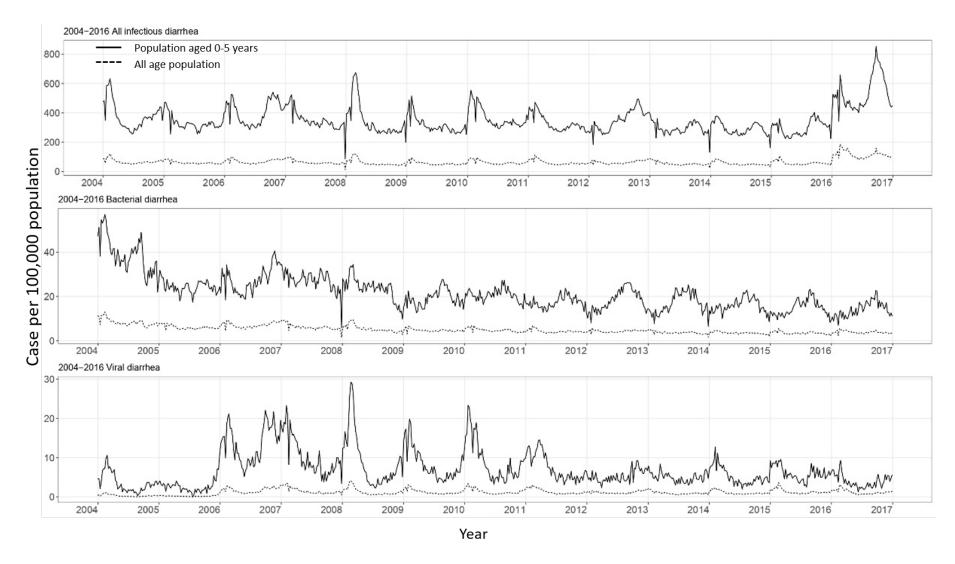


Figure 1. Weekly trend of cause-specific diarrhea stratified by sex and age in Taiwan from 2004 to 2016

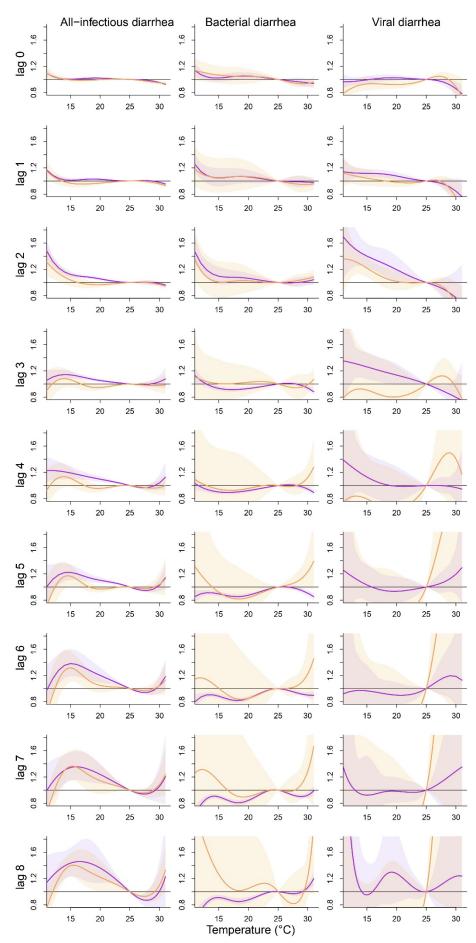


Figure 2. Pooled relative risks of age-cause-lag-specific diarrhea associated with weekly average temperature in Taiwan from 2004 to 2016 (Purple= all age; Yellow= under 5 years)

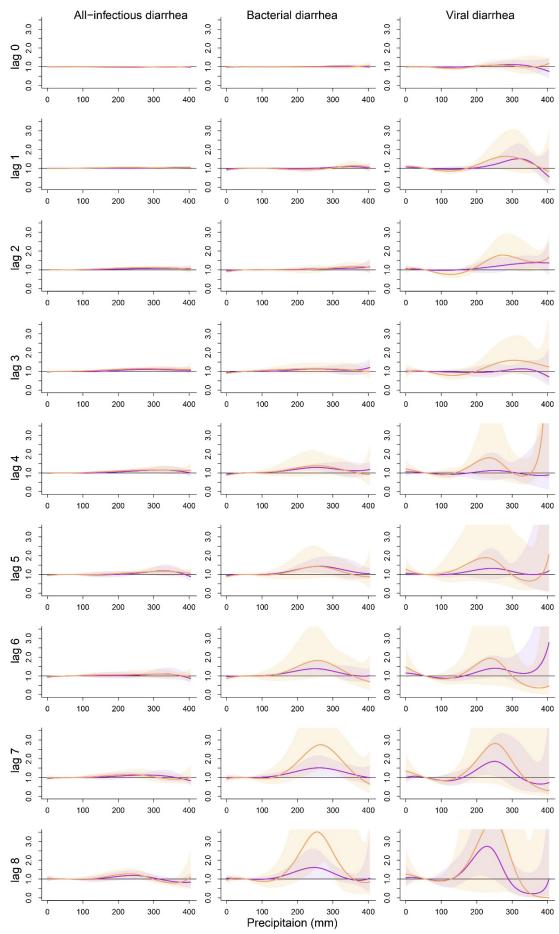
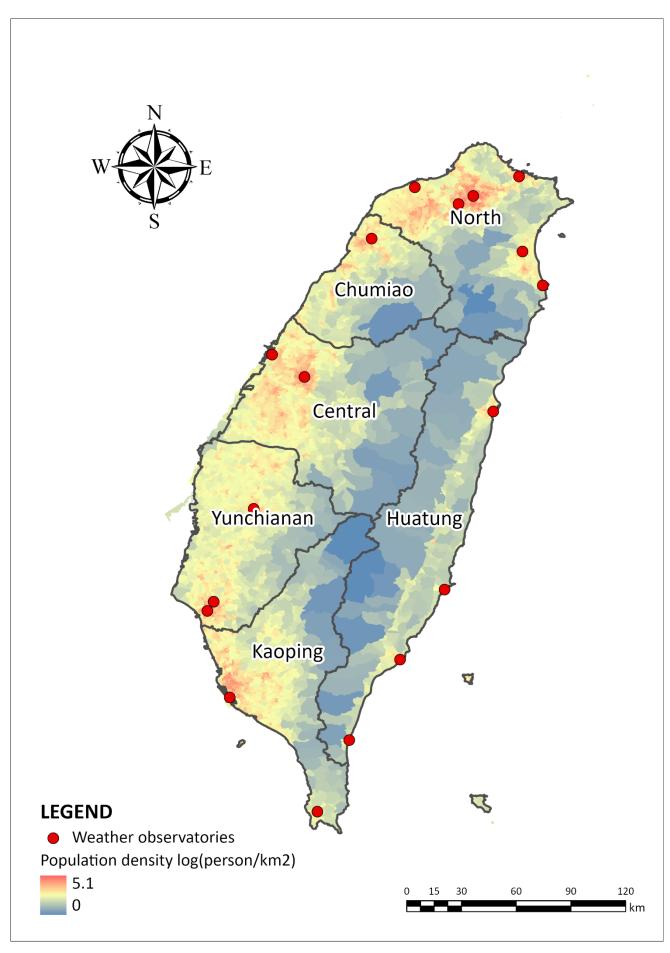
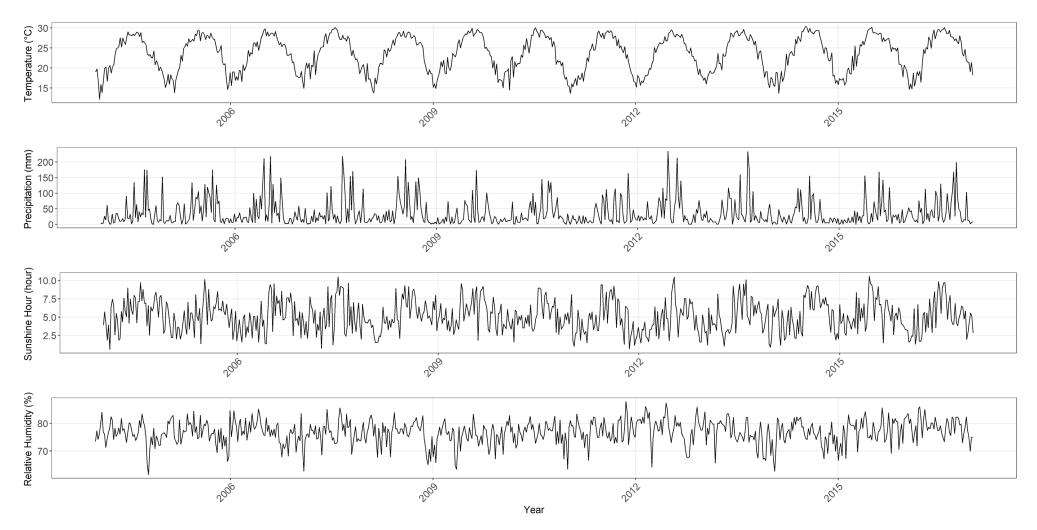


Figure 3. Pooled relative risks of age-cause-lag-specific diarrhea associated with weekly cumulative precipitation in Taiwan from 2004 to 2016 (Purple= all age; Yellow= under 5 years

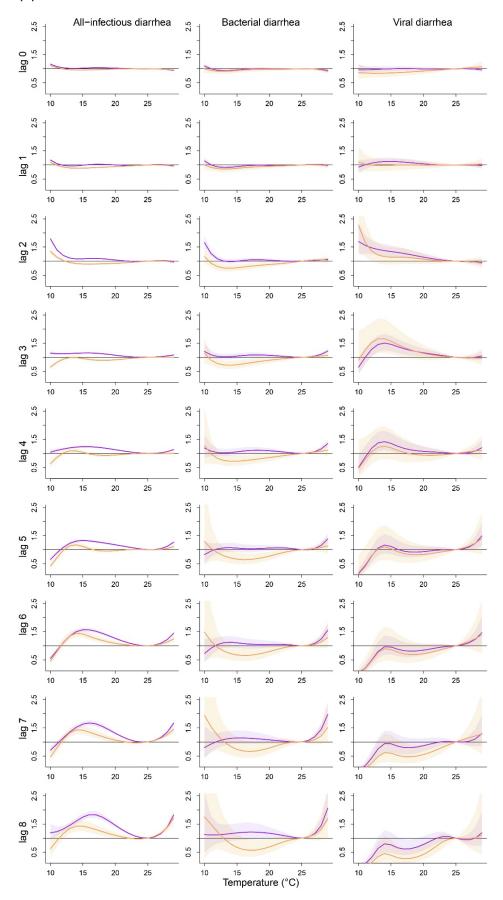


Supplementary Figure S1. Location of study area

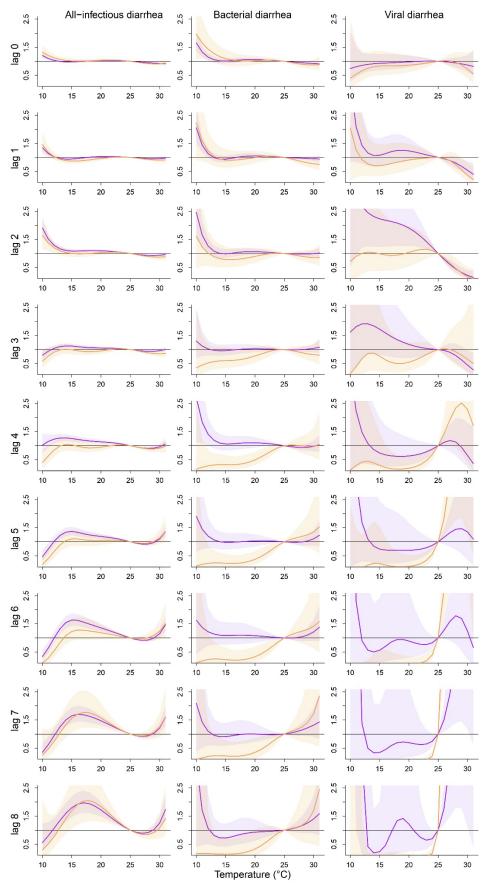


Supplementary Figure S2. Trend of environmental factors from 2004 to 2016 in Taiwan

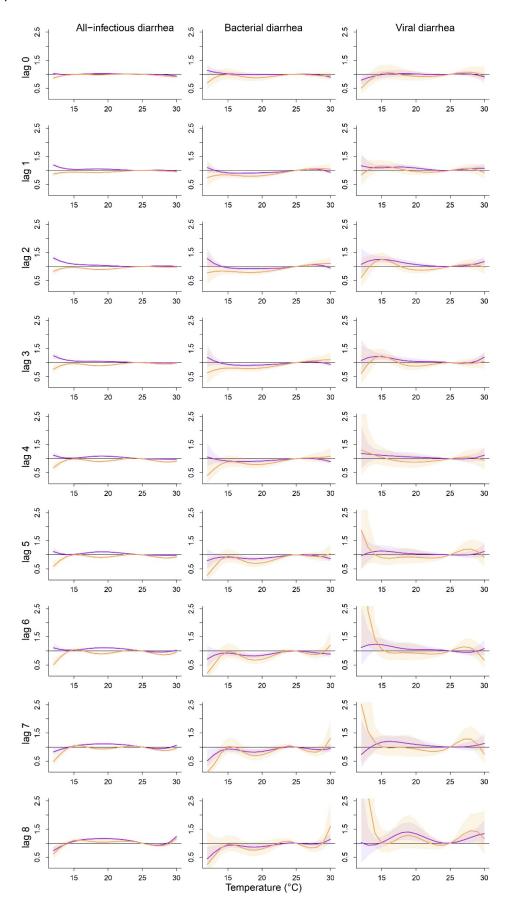
(a) North



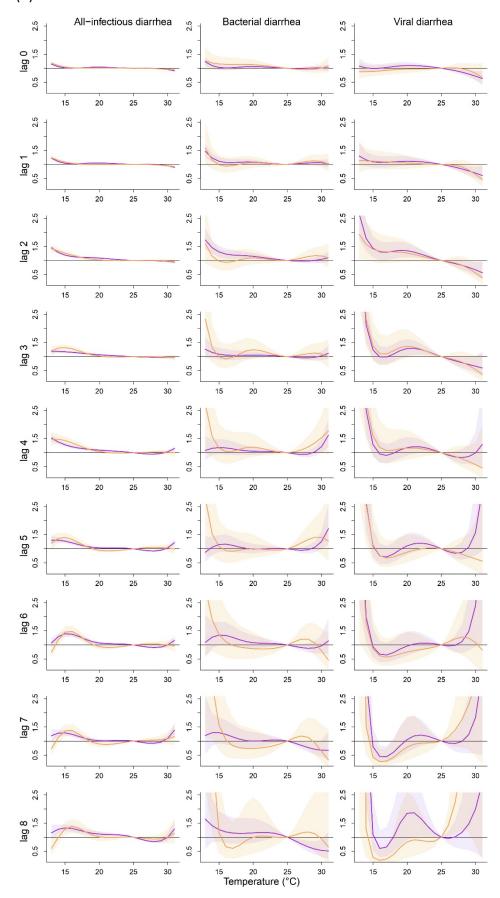
(b) Chumiao



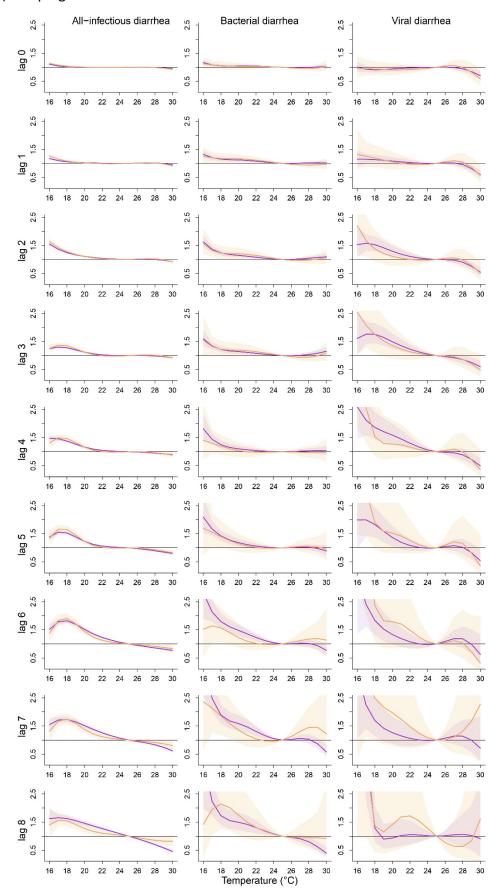
(c) Central



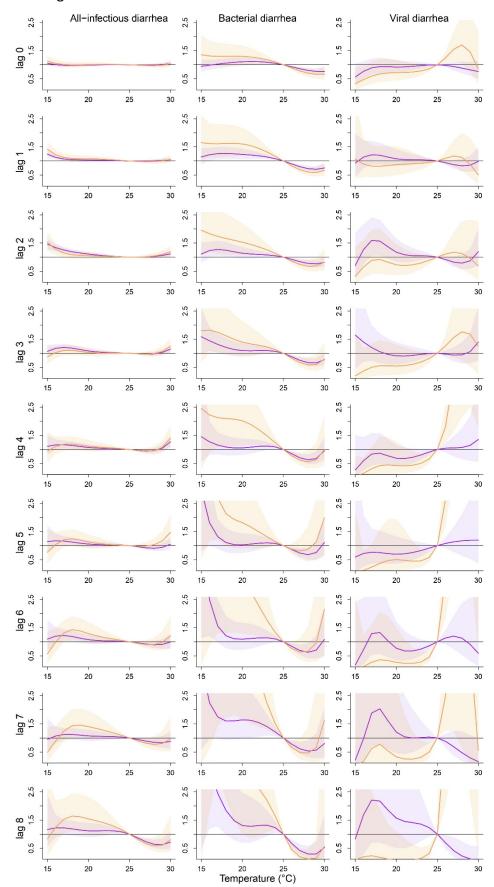
(d) Yunchianan



(e) Kaoping

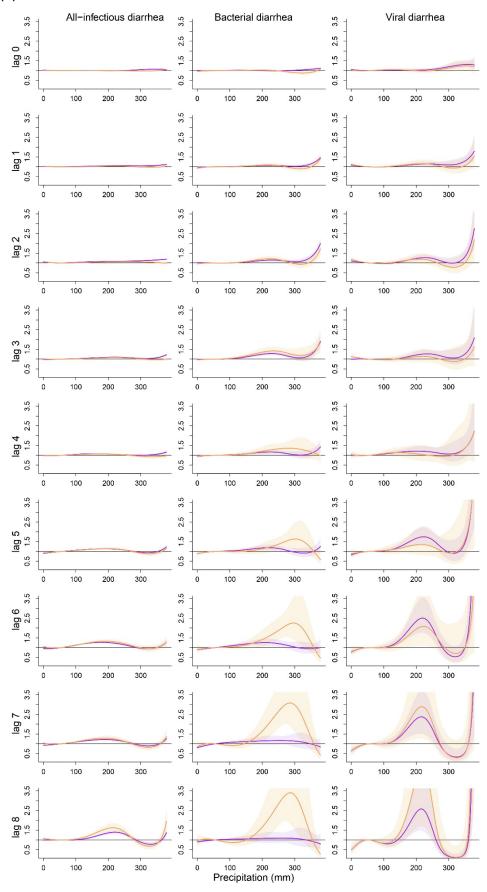


(f) Huatung

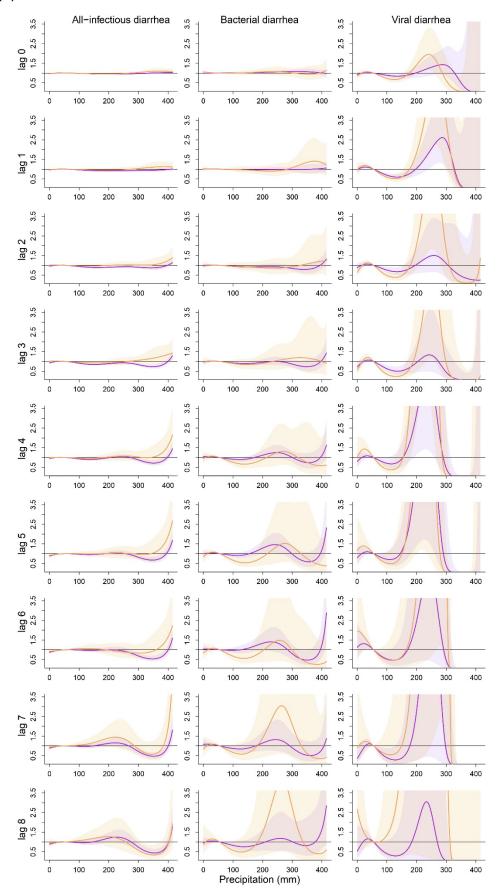


Supplementary Figure S3. The relative risk of age-, area-, cause-, and lag-specific diarrhea associated with weekly average temperature in six regions of Taiwan, including (a) North, (b) Chumiao, (c) Central, (d) Yunchianan, (e) Kaoping, and (f) Huatung region (Purple= all age; Yellow= under 5 years)

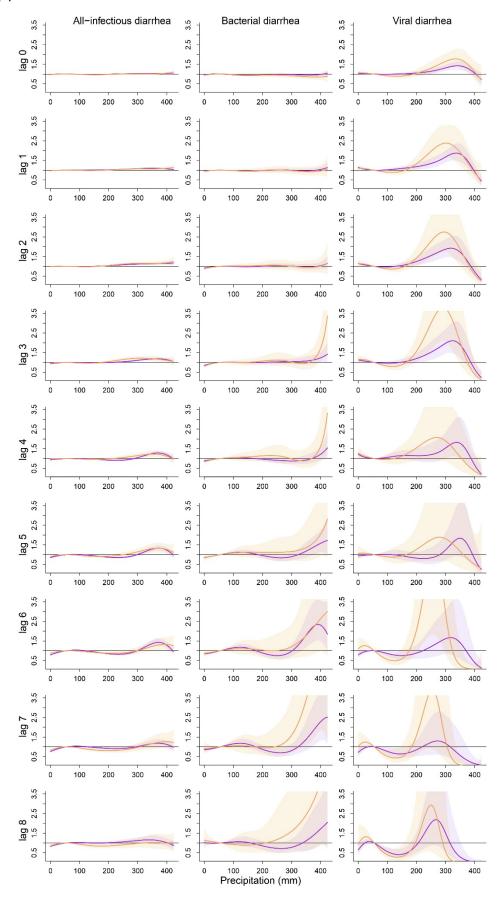
(a) North



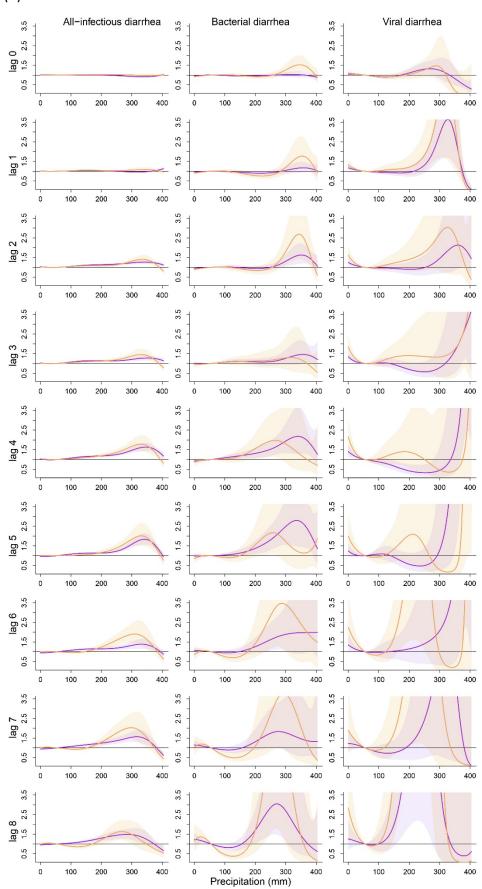
(b) Chumiao



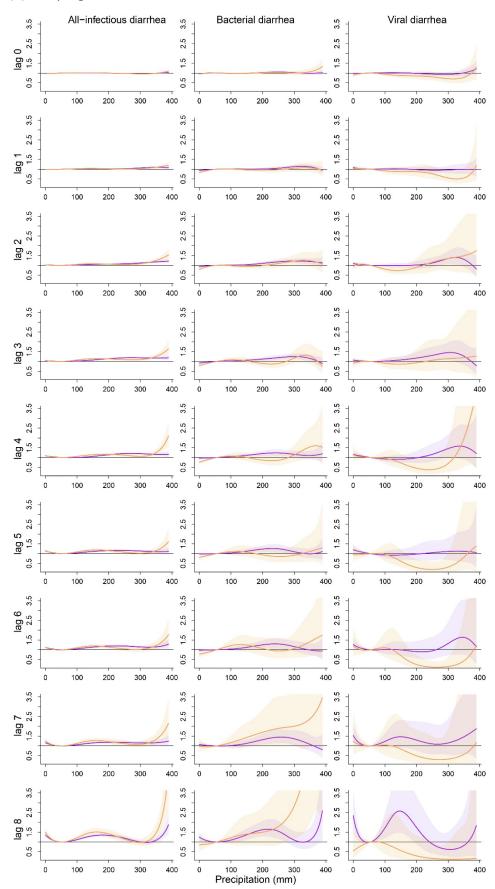
(c) Central



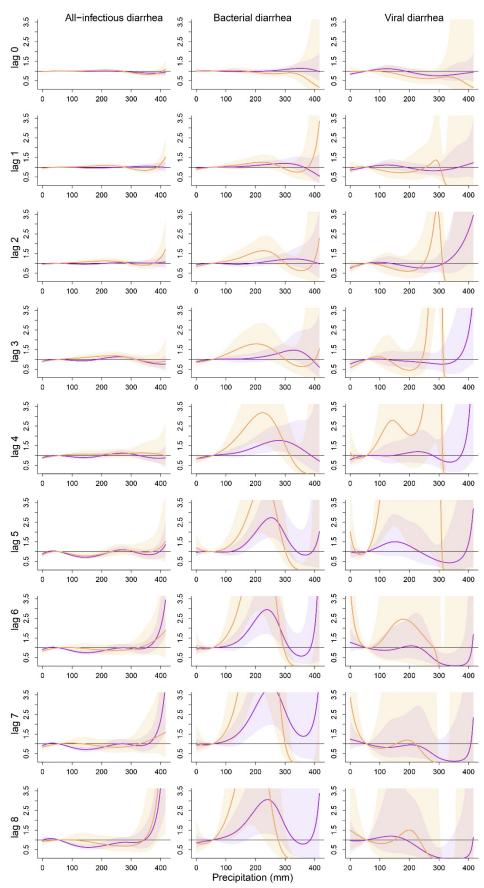
(d) Yunchianan



(e) Kaoping



(f) Huatung



Supplementary Figure S4. The relative risk of age-, area-, cause-, and lag-specific diarrhea associated with weekly cumulative precipitation in six regions of Taiwan, including (a) North, (b) Chumiao, (c) Central, (d) Yunchianan, (e) Kaoping, and (f) Huatung (Purple= all age; Yellow= under 5 years)

Supplementary Table S1. Meta-analyses estimated cumulative relative risk (RR) and 95% confidence interval (CI) of age-cause-lag-specific diarrhea associated with the extreme temperatures in six regions of Taiwan

	All infectious diarrhea		Bacterial o	diarrhea	Viral diarrhea		
Lag week	5th percentile (15.30 °C)						
	all age	under 5	all age	under 5	all age	under 5	
0	1.01 (0.99–1.02)	1.00 (0.97–1.03)	1.03 (0.97–1.08)	1.08 (0.95–1.22)	1.00 (0.94–1.06)	0.93 (0.83–1.04)	
1	1.01 (0.98–1.05)	0.97 (0.91–1.03)	1.05 (0.92–1.20)	1.06 (0.82–1.37)	1.12 (1.06–1.19)	1.04 (0.93–1.17)	
2	1.13 (1.09–1.17) 1.04 (1.10 (0.98–1.24)	1.01 (0.77–1.34)	1.41 (1.24–1.60)	1.22 (1.08–1.39)	
3	1.14 (1.09–1.20)	1.07 (0.96–1.20)	0.94 (0.90–0.97)	1.02 (0.74–1.41)	1.27 (1.08–1.49)	0.90 (0.54–1.49)	
4	1.20 (1.11–1.30)	1.12 (0.98–1.27)	0.91 (0.87–0.94)	0.95 (0.57–1.60)	1.13 (0.86–1.49)	0.77 (0.41–1.46)	
5	1.23 (1.12–1.35)	1.17 (1.03–1.34)	0.90 (0.87–0.94)	0.92 (0.55–1.55)	1.04 (0.80–1.35)	0.64 (0.30–1.37)	
6	1.39 (1.20–1.61)	1.32 (1.12–1.57)	0.89 (0.86–0.93)	1.01 (0.50–2.05)	0.97 (0.69–1.36)	0.45 (0.14–1.51)	
7	1.35 (1.15–1.58)	1.38 (1.17–1.62)	0.90 (0.87–0.94)	1.14 (0.51–2.60)	0.93 (0.57–1.53)	0.29 (0.05–1.80)	
8	1.44 (1.24–1.67)	1.42 (1.25–1.61)	0.92 (0.88–0.96)	1.30 (0.43–3.97)	0.96 (0.63–1.45)	0.20 (0.04–1.14)	
99th percentile (31.07 °C)							
0	0.94 (0.93-0.96)	0.95 (0.93–0.97)	0.95 (0.89–1.02)	0.96 (0.90–1.03)	0.86 (0.77–0.97)	0.80 (0.62–1.04)	
1	0.99 (0.97–1.00)	0.94 (0.92–0.97)	0.99 (0.92–1.06)	0.96 (0.87–1.06)	0.85 (0.69–1.04)	0.66 (0.45–0.96)	
2	0.99 (0.96–1.02)	0.96 (0.93–0.99)	1.03 (0.96–1.09)	1.08 (0.99–1.17)	0.77 (0.51–1.18)	0.62 (0.40–0.97)	
3	1.04 (0.95–1.14)	0.99 (0.87–1.13)	0.94 (0.91–0.98)	1.04 (0.92–1.19)	0.80 (0.59–1.10)	0.84 (0.62–1.13)	
4	1.04 (0.94–1.16)	0.99 (0.86–1.14)	0.95 (0.92–0.99)	1.21 (0.96–1.53)	0.97 (0.77–1.23)	1.24 (0.51–2.99)	
5	1.03 (0.94–1.13)	1.09 (0.89–1.34)	0.91 (0.87–0.95)	1.32 (0.97–1.79)	1.20 (0.91–1.59)	2.07 (0.49-8.72)	
6	1.05 (0.93–1.18)	1.10 (0.92–1.32)	0.91 (0.87–0.95)	1.35 (0.78–2.33)	1.19 (0.76–1.87)	2.14 (0.47–9.83)	
7	1.06 (0.82-1.39)	1.18 (0.92–1.51)	0.93 (0.89–0.97)	1.49 (0.80–2.79)	1.29 (0.54–3.09)	5.03 (0.23–112)	
8	1.01 (0.70–1.48)	1.24 (0.99–1.56)	1.07 (1.02–1.13)	1.65 (0.97–2.83)	1.24 (0.46–3.33)	15.57 (0.73–332)	

Supplementary Table S2. Meta-analyses estimated cumulative relative risk (RR) and 95% confidence interval (CI) of age-cause-lag-specific diarrhea associated with the extreme precipitations in six regions of Taiwan

	All infectious diarrhea		Bacterial d	iarrhea	Viral diarrhea		
Lag week	5th percentile (0 mm)						
	all age	under 5	all age	under 5	all age	under 5	
0	1.00 (0.99–1.02)	0.99 (0.98–1.00)	0.99 (0.98–1.00)	0.96 (0.93–1.00)	1.01 (0.95–1.06)	0.99 (0.90–1.08)	
1	1.00 (0.98-1.03)	1.00 (0.99–1.01)	0.97 (0.95–1.00)	0.91 (0.86–0.96)	1.08 (1.01–1.15)	1.11 (0.99–1.24)	
2	1.02 (0.99–1.05)	1.02 (1.00-1.04)	0.97 (0.94–1.00)	0.90 (0.83-0.98)	1.08 (0.97–1.20)	1.03 (0.81–1.33)	
3	0.98 (0.94–1.02)	1.00 (0.96–1.04)	0.94 (0.90-0.98)	0.91 (0.82–1.00)	1.01 (0.86–1.19)	0.96 (0.68–1.37)	
4	0.99 (0.95–1.04)	1.01 (0.95–1.07)	0.94 (0.88-1.00)	0.89 (0.80–0.98)	1.06 (0.87–1.29)	1.21 (0.88–1.67)	
5	0.96 (0.89–1.03)	0.96 (0.88–1.05)	0.95 (0.89–1.02)	0.89 (0.78–1.02)	1.07 (0.89–1.27)	1.29 (0.90–1.85)	
6	0.95 (0.89–1.02)	0.97 (0.89–1.07)	0.97 (0.88–1.07)	0.87 (0.75–1.01)	1.16 (0.94–1.45)	1.48 (0.87–2.52)	
7	0.96 (0.89–1.04)	1.00 (0.88–1.13)	1.00 (0.88–1.12)	0.92 (0.76–1.12)	1.00 (0.72–1.41)	1.36 (0.83–2.23)	
8	1.02 (0.88–1.18)	1.04 (0.87–1.25)	1.04 (0.91–1.20)	0.94 (0.75–1.19)	1.07 (0.65–1.75)	1.26 (0.60–2.64)	
	99th percentile (290 mm)						
0	0.99 (0.97–1.02)	1.00 (0.98–1.01)	1.03 (1.00–1.06)	0.99 (0.92–1.07)	1.12 (0.93–1.35)	1.06 (0.80–1.41)	
1	1.02 (0.98–1.06)	1.04 (1.01–1.07)	1.05 (1.01–1.09)	1.01 (0.94–1.08)	1.43 (0.98–2.09)	1.64 (0.88–3.05)	
2	1.08 (1.01–1.16)	1.13 (1.07–1.19)	1.07 (0.97–1.17)	1.09 (0.95–1.25)	1.28 (0.97–1.68)	1.76 (1.05–2.93)	
3	1.11 (1.01–1.22)	1.15 (1.05–1.27)	1.11 (0.95–1.30)	1.14 (0.90–1.45)	1.08 (0.88–1.34)	1.58 (0.89–2.81)	
4	1.15 (1.03–1.28)	1.16 (1.00–1.35)	1.25 (1.00–1.56)	1.33 (0.91–1.93)	1.07 (0.72–1.60)	1.17 (0.54–2.54)	
5	1.15 (1.00–1.32)	1.15 (0.96–1.38)	1.40 (0.99–1.97)	1.35 (0.87–2.10)	1.21 (0.89–1.65)	1.14 (0.35–3.70)	
6	1.09 (0.94–1.26)	1.10 (0.88–1.37)	1.30 (1.03–1.65)	1.68 (1.00–2.85)	1.29 (0.84–1.97)	1.21 (0.41–3.63)	
7	1.13 (0.98–1.31)	1.07 (0.82–1.39)	1.47 (1.07–2.03)	2.56 (1.55–4.25)	1.49 (0.68–3.29)	2.16 (0.44–10.76)	
8	1.10 (0.93–1.30)	1.06 (0.87–1.28)	1.41 (1.01–1.97)	2.77 (1.60–4.79)	0.99 (0.38–2.54)	2.51 (0.33–19.33)	

Table 1. Means and ranges of weekly cause-specific diarrhea and weather variables in six region of Taiwan from 2004 to 2016

Characteristics	Mean (SD)	Minimum	P5*	P50**	P99***	Maximum
All age						
All infectious diarrhea	2,266 (2059)	59	171	1,712	8,854	14,639
Bacterial diarrhea	71 (102.75)	0	12	117	816	1,465
Viral diarrhea	17 (28.56)	0	0	18	229	328
Under 5 years						
All infectious diarrhea	564 (504)	17	53	461	2,122	3,799
Bacterial diarrhea	35 (43.67)	0	3	20	209	448
Viral diarrhea	11 (14.29)	0	0	6	69	100
Weather variables						
Average temperature (°C)	23.53 (4.65)	9.34	15.30	24.38	30.18	31.07
Precipitation (mm)	36.20 (57.60)	0	0	13.31	290.4	404
Sunshine hour (hour)	5.16 (2.52)	0	1.14	5.13	10.60	12.14
Relative humidity (%)	76.86 (5.19)	54.71	67.81	77.08	88.42	93.57

Note: P5, P50 and P99 represent the measurements at 5th, 50th, and 99th percentiles