Effects of ambient temperature on atopic dermatitis and attributable health burden: A 6-year time-series study in Chengdu, China

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Background. Despite increasing public concerns about the widespread health effects of climate change, the impacts of ambient temperature on atopic dermatitis (AD) remain poorly understood.

Objectives. We aimed to explore the effect of ambient temperature on AD and to estimate the burdens of AD attributed to extreme temperature.

Methods. Data on outpatients with AD and climate conditions in Chengdu, China were collected. A distributed lag nonlinear model (DLNM) was adopted to explore the association between daily mean temperature and AD outpatient visits. Subgroup analysis was used to identify vulnerable populations. Attributable burden was estimated by the epidemiological attributable method.

Results. We analyzed 10747 outpatient visits from AD patients at West China Hospital in Chengdu between January 1, 2015, and December 31, 2020. Both low (˂19.6 °C) and high temperatures (˃25.3 °C) were associated with increased AD outpatient visits, with the increase being more pronounced at low temperature, as evidenced by a 160% increase in visits when the temperature dropped below zero from the minimum mortality temperature (22.8 °C). Children and males were the most susceptible populations. Approximately 25.4% of AD outpatient visits were associated with temperatures, causing an excessive 137161.5 US dollars of health care expenditures during this 6-year period.

Conclusions. Both high and low temperatures, particularly low temperatures, were significantly associated with an increased risk of AD, with children and males showing the highest associations. Extreme environmental temperature has been identified as one of the major factors promoting the development of AD. However, individual patient-level exposures still needed to be investigated in future studies to confirm the causality between temperature and AD.

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37 The authors declare there are no competing interests.

38

39 **Author Contributions**

40 ● Zerong Chen and Mengmeng Li conceived and designed the experiments, performed the

41 experiments, analyzed the data, prepared figures and/or tables, wrote the paper, reviewed

42 drafts of the paper and approved the final draft.

43 ● Tianjiao Lan, Yiyi Wang, Xingli Zhou, Wei Dong and Gong Cheng analyzed the data,

44 prepared figures and/or tables, and approved the final draft.

45 ● Liangliang Cheng and Wei Li conceived and designed the experiments, analyzed the data,

46 authored or reviewed drafts of the paper, and approved the final draft.

47

48 **Ethical approval**

49 The studies involving human participants were reviewed and approved by Ethics Committee on

50 Biomedical Research, West China Hospital of Sichuan University (2021 Review No.1963).

51

52 **Data Availability**

53   The following information was supplied regarding data availability:

54   The raw measurements are available in the Supplementary File.

Abstract

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Methods. Data on outpatients with AD and climate conditions in Chengdu, China were collected. A distributed lag nonlinear model (DLNM) was adopted to explore the association between daily mean temperature and AD outpatient visits. Subgroup analysis was used to identify vulnerable populations. Attributable burden was estimated by the epidemiological attributable method.

Results. We analyzed 10747 outpatient visits from AD patients at West China Hospital in Chengdu between January 1, 2015, and December 31, 2020. Both low (<19.6 °C) and high temperatures (>25.3 °C) were associated with increased AD outpatient visits, with the increase being more pronounced at low temperature, as evidenced by a 160% increase in visits when the temperature dropped below zero from the minimum mortality temperature (22.8 °C). Children and males were the most susceptible populations. Approximately 25.4% of AD outpatient visits were associated with temperatures, causing an excessive 137161.5 US dollars of health care expenditures during this 6-year period.

Conclusions. Both high and low temperatures, particularly low temperatures, were significantly associated with an increased risk of AD, with children and males showing the highest associations. Extreme environmental temperature has been identified as one of the major factors promoting the development of AD. However, individual patient-level exposures still needed to be investigated in future studies to confirm the causality between temperature and AD.

Keywords: Atopic dermatitis, Temperature, Attributable burden, Climate change.

82

83

84 **Introduction**

85 Climate change represents one of the greatest global health threats in the 21st century. It affects

86 many of the social and environmental determinants of public health, and contributes directly and

87 indirectly to the high morbidity and mortality of many diseases worldwide (*IPCC*). As the first

88 barrier contacting the environment, skin is particularly vulnerable to climate change and extreme

89 weather events (*Sun & Rosenbach,2021*). Atopic dermatitis (AD), also known as atopic eczema,

90 is a pruritic chronic inflammatory skin disease with serious effects on patients' quality of life

91 (*Andersen et al.,2017; Marciniak et al.,2017*). The global incidence of AD has increased by 2 to

92 3-fold in the past half-century while the pathogenesis of AD remains undefined (*Asher et*

93 *al.,2006*).

94

95 Recently, an increasing number of studies have suggested that the number of AD patients is

96 associated with exceptionally low or high air temperature or both. For instance, studies from

97 developed countries such as the United States have found that the risk of AD increased in hot

98 seasons, such as May and June, and cold seasons, such as October and January (*Fleischer,2019;*

99 *Silverberg et al.,2013*). In Denmark, it was found that when the monthly temperature decreased

100 by 1 °C, 2 more (95% CI:1-4) monthly hospitalizations of AD were observed, based on the

101 inpatient data from nationwide healthcare registries from 1977 to 2012 (*Hamann et al.,2018*).

102 Similar findings have also been reported from low-income countries. Higher temperatures were

103 found to be associated with a greater number of AD patients in Nigeria (*Ibekwe & Ukonu,2019*),

104 and high temperatures also accelerate diffusion of air pollutants, which worsen population health

105 and lead to more outpatient visits of AD in Beijing, China (*Guo et al.,2019*).

106

107   Despite the wide recognition of extreme temperatures as risk factors for AD, high-quality

108   evidence with appropriate statistical methods remains insufficient. Heat typically exhibits a

109   nonlinear and lagged relationship with health outcomes (*Gasparrini et al.,2010*). In prior studies

110   of temperature and AD, linear regression models were most commonly used and lagged effects

111   rarely considered, which may lead to an overestimation or underestimation of exposure-response

112   relationship. As an extension of traditional distributed lag models, the distributed lag nonlinear

113   model (DLNM) enables simultaneous estimation of a variety of nonlinear functions of

114   temperature associations as well as nonlinear effects across lag periods, based on a bi-

115   dimensional space of 'cross-basis' functions. DLNM has become one of the most widely used

116   models in environmental health studies over the past decades (*Gasparrini et al.,2010; Zhao et*

117   *al.,2021*).

118

119   Additionally, there is also a lack of clear and practical information that can help patients, doctors

120   and health administrators reduce the risk. To inform health policy and personalized clinical

121   practice, much more effort is needed to identify specific populations vulnerable to extreme

122   temperatures, illustrate the boundary between favorable and unfavorable temperatures for

123   preventing AD, and quantify the burden of AD caused by extreme temperatures with an

124   advanced and well-established analysis structure (*Gasparrini et al.,2015; Gasparrini &*

125   *Leone,2014*). Without accurately addressing these issues, it is difficult to propose and develop

126   appropriate, effective prevention and control measures in relation to climate change, especially

127   amid rapidly intensifying global climate change (*Patz et al.,2014*).

128

129   As one of the largest countries, China has been facing intense challenges to public health due to

130   climate change, including rising morbidity and health care burden for many diseases, including

131   AD (*Guo et al.,2019*). There is a pressing need to comprehend the effects of climate change on

132   human health and diseases in China. The primary goal of this study is to estimate the effects of

133   ambient air temperature on AD and the corresponding attributable burden. To achieve this goal,

134   we focused on AD and climate conditions in Chengdu, a megacity in Western China with a

135   resident population of over 16 million. We demonstrated (i) the association of hot and cold

136   ambient temperatures with the risk of AD, (ii) the temperature thresholds associated with

137   increased AD morbidity, (iii) the populations most vulnerable to extreme temperatures, and (iv)

138   the estimated health and economic burden of AD associated with extreme temperatures.

139

140   **Methods**

141   **Study site and meteorological data collection**

142   This study was approved by the Ethics Committee of the West China Hospital of Sichuan

143   University (2021 Review No.1963). The study is confined to a single geographic region –

144   Chengdu, the capital city of Sichuan Province and the largest city in western China, with a

145   resident population of approximately 16 million. Chengdu is in a basin area with a subtropical

146   monsoon climate. Its annual average temperature was 16.5 °C between 2015 and 2020, with an

147   average of 24.9 °C in the summer and 7.0 °C in the winter.

148

149   The time frame of this study spans from January 1, 2015 to December 31, 2020. Meteorological

150   data (including daily mean temperature, relative humidity, sunshine duration, atmospheric

151   pressure and precipitation) during this period in Chengdu were obtained from the National

152   Meteorological Data Sharing Platform (http://data.cma.cn/). Air quality data (including $PM_{2.5}$,

153   NO_2 and SO_2) during this period were obtained from the National Urban Air Quality Real-time

154   Publishing Platform (http://106.37.208.233:20035/). These pollution and meteorological

155   covariates were chosen as previous studies have reported that these factors can be important

156   confounders in identifying the real association between temperature and AD (*Guo et al.,2019;*

157   *Kantor & Silverberg,2017; Wang et al.,2021*). In addition, we also discussed with clinical

158   experts and meteorologists to select the possible covariates. Approximately 2.7% of the

159   meteorological data contained missing values, which were imputed by the linear interpolation

160   approach, as commonly used in meteorology (*Zhang et al.,2019*).

161

162   **Epidemiological and clinical data collection**

163   All patients were outpatients diagnosed with AD during the same period described above in the

164   Department of Dermatology, West China Hospital of Sichuan University, Chengdu, China. As

165   the largest hospital in western China with more than 4000 beds, West China Hospital ranks

166   among the very top hospitals in China with high performance in skin disease management. From

167   all these patients, we collected information on dates for outpatients diagnosed with AD,

168   demographic characteristics, clinical diagnosis, current address, and related medical

169   expenditures.

170

171   The AD outpatients were included by both searching the keywords ("atopic dermatitis" and

172   "atopic eczema") in the Outpatient Information System. The AD cases in our study included L20

173   among the ICD-10 code. Patients of all ages were included with no gender restriction and were

174   excluded if they did not physically reside in Chengdu throughout the study period. The sample

175   size is sufficient to ensure the statistical power in the study (R code for estimating statistical

176   power in the Supplemental Information).

177

178   **Statistical analysis**

179   This is an ecological study with a time-series approach. We first constructed a distributed lag

180   nonlinear model (DLNM) to assess the effects of ambient air temperature on AD, and determine

181   the temperature thresholds that cause an increased risk of AD. As the probability for hospital

182   visits for AD is small, a quasi-Poisson regression was applied, allowing for over-dispersion with

183   the distributed lag nonlinear model (DLNM). This model is widely used in environmental and

184   health studies, due to its ability to simultaneously capture and assess the nonlinear exposure-

185   response relationships and lagged effects of environmental factors on health outcomes

186   (*Bhaskaran et al.,2013; Gasparrini et al.,2010*). The model is expressed as follows:

187

188       $Log[E(Y_t)] = \alpha + \beta Temp_{t,l} + NS(RH_t,3) + NS(SH_t,3) + NS(SP_t,3) \ + \qquad\qquad NS(TP_t,3) \ +$

189     $\theta PM_{2.5} \ + \ NS(Time,7*6) + \gamma DOW$

190

191   where Y_t denotes the daily counts of outpatient visits at day t, and $E(Y_t)$ is the expected number of

192   outpatient visits; $Temp_{t,l}$ is a cross-basis matrix assessing the nonlinear and lag effects of air

193   temperature over the current day (lag0) to the maximum lag at l days (lag$l$). We found that the

194   lag effect of temperature was statistically significant in 7 days, and consequently 7 days was

195   chosen as the maximum lag. In addition, the model had the best AIC (Akaike Information

196   Criterion) when the lag days was set for 7 days. We used natural cubic spline function for

197   considering the non-linear effects of temperature, and 4 degrees of freedom (df) was set based on

198   the least AIC.

199

200   *NS* denotes the natural cubic spline function. $NS(RH_t,3)$, $NS(SH_t,3)$, $NS(SP_t,3)$ and $NS(TP_t,3)$ were

201   used to control the potential confounding effects of relative humidity, sunshine duration, surface

202   air pressure and total precipitation, respectively. They were set with natural cubic splines of 3

203   degrees of freedom (df) based on AIC for quasi-Poisson models. $PM_{2.5}$ represents the daily 24-

204   hour concentrations ($\mu g/m^3$) of particulate matter with a diameter of fewer than 2.5 micrometers.

205   As different air pollutants are highly correlated, only $PM_{2.5}$was included since it was the most

206   important contributor to air pollution in Chengdu. $NS(Time,7*6)$ is a natural cubic spline of time

207   with 7 degrees of freedom per year (all 6 years of the study) to control the seasonal and long-

208   term trends. Based on previous methodological and epidemiological research, 7 degrees of

209   freedom per year is sufficient to adjust for seasonal and long-term trends (*Gasparrini et al.,2010;*

210   *Meng et al.,2021; Wang et al.,2021; Zhao et al.,2021*). *DOW* denotes the day of the week and was

211   used for controlling with-in-week variation effects. The parameter α is the intercept. θ is the

212   coefficient parameter of PM2.5. β is the estimated coefficient, which was finally converted to the

213   risk ratio (RR) to express the effects of temperature on AD.

214

215   Following completion of the analysis above, the optimal temperature range for preventing AD

216   was determined based on the temperatures where the effects on the number of AD patients were

217   not statistically significant. Additionally, subgroup analysis was conducted to identify the

218   populations most vulnerable to temperature change. In this study, children were defined as age $\leq$

219   18 years and adults as age >18 years. Specifically, we first divided the raw data into four

220   different subgroups according to sex (male and female) and age (children and adults). Data from

221   each subgroup included the daily number of AD visits, daily temperature, and other covariates.

222   Then, we analyzed the exposure-response associations between temperature and AD in different

223   subgroups using a unified DLNM model. Finally, we compared the exposure-response curves

224   and AFs in different subgroups and identified individuals who are more susceptible to extreme

225   temperatures.

226

227   In addition, we calculated the temperature-related attributable burden for AD according to the

228   method described in previous literature (*Gasparrini & Leone,2014*). The attributable fraction

229   (AF) and attributable number (AN) were used to represent the percentage and number of AD

230   patients affected by extreme temperature. The corresponding empirical confidence intervals

231   (eCIs) were estimated with Monte Carlo simulations (*Zhao et al.,2019*). The attributable

232   economic burden was estimated using the AN multiplied by the average health care expenditures

233   for each patient.

234

235   **Sensitivity analysis**

236   Sensitivity analysis was performed to test the robustness of the results. For relative air humidity,

237   sunshine duration, atmospheric pressure and precipitation, dfs in the spline function were set

238   from 2 to 5. For the time trend, dfs in the spline function were set at 3, 5, 7 and 9 respectively.

239   The different maximum lag times for temperature were also set at 3, 5, 7 and 9 days. We also

240   conducted DLNM by adjusting SO2 or NO2, respectively. In addition to the AIC, we used the

241   BIC to select the appropriate dfs and lag time, as the BIC penalizes the number of parameters in

242   the model to a greater extent than AIC.

243

244   All statistical analyses were performed using R software (version 3.6.3, https://www.R-

245   project.org) with the R package 'dlnm' (version 2.3.2). A two-tailed P value < 0.05 was

246   considered statistically significant.

247

248   **Results**

249   **Descriptive statistics**

250   There were 10747 outpatient visits from AD patients between 2015 and 2020 in our hospital,

251   including 71.1% of children's visits and 57.0% of male patient visits. Table 1 illustrates the

252   descriptive statistics of AD outpatient visits, meteorological indicators and air pollutant

253   concentrations. The average number of daily visits was 5.0, with 3.6 for children and 2.9 for

254   male patients. The mean daily temperature, relative humidity, sunshine duration, surface air

255   pressure, total precipitation, PM2.5, NO2, and SO2 were 16.5℃, 81.0%, 2.7h, 92.6kpa, 3.0mm,

256   48.1μg/m^3, 41.2μg/m^3, and 11.0μg/m^3, respectively. The correlations among meteorological

257   factors and air pollution are shown in Table S1.

258

259   Fig. 1 presents the distribution of the monthly average daily mean temperature and monthly

260   mean number of AD outpatient visits between 2015 and 2020. The monthly average daily mean

261   temperature ranged from 6.1 °C to 25.4 °C, with an overall mean of 16.4 °C during the 6-year

262 period. The peak of AD outpatient visits occurred in the three coldest months (from November to

263 January), followed by a lower peak in August, the hottest month. Scatter plots between AD and

264 other meteorological indicators/air pollutants are in the Appendix (Fig. S1-S8).

265

266 **Association between temperature and the number of AD outpatient visits**

267 Fig. 2 shows the overall cumulative effects of temperature on the number of outpatient visits in

268 all AD patients. In general, the exposure-response curve followed a shallow U-shape, indicating

269 that both high and low temperatures increased the risk of AD. Significantly strong effects were

270 observed at temperatures below 19.6 °C and above 25.3 °C. The effect was stronger at cold

271 temperatures than at hot temperatures. When the temperature dropped below zero the risk of AD

272 almost doubled (RR= 2.6, 95% eCI: 1.4-5.0) compared with the centering temperature of 22.8 °C

273 (same as the minimum mortality temperature described later). In addition, low-temperature

274 effects lasted for 7-8 days, and high-temperature effects lasted for 3-4 days (Fig. S9-S10).

275

276 **Populations vulnerable to extreme temperatures**

277 Fig. 3 shows the association between daily mean temperature and the number of AD outpatient

278 visits in different patient groups. The exposure-response curve for the child group showed a U-

279 shape similar to the curve for all patients in Fig. 2, suggesting that both high temperature and low

280 temperature increased the risk of AD. However, this effect was not statistically significant in the

281 adult group. When the patients were divided by sex, low temperature increased the risk of AD in

282 both the male and female groups, while high temperature increased the risk only in the female

283 group.

284

285 **Health burden of AD attributed to extreme temperatures**

286 The health burden of AD outpatient visits attributed to extreme temperatures is presented in

287 Table 2. Overall, 25.4% (AF = 25.4%; 95% eCI: 9.2%, 36.0%) of the AD outpatient visits were

288   attributed to extreme temperatures, corresponding to approximately 2724 visits (AN = 2724.4,

289   95% eCI: 955.7, 3909.2) during the study period. Among the 10747 visits, 22.4% were caused

290   by low temperature and 3.0% by high temperature, leading to an estimated health care

291   expenditures of 932698.3 RMB (137161.5 US dollars) for AD patients in the study period.

292

293   Regarding the attributable burden for different patient groups, an estimated 29.3% (AF = 29.3%,

294   95% eCI: 11.5%, 40.6%) of the AD outpatient visits among children were associated with

295   extreme temperatures, with 25.8% of them (AF = 25.8%, 95% eCI: 8.9%, 38.0%) being

296   associated with low temperature. For male patients, an estimated 28.7 % (AF = 28.7%, 95% eCI:

297   9.1%, 41.3%) of the AD outpatient visits were attributed to low temperature, whereas for

298   females, 4.7 % (AF = 4.7%, 95% eCI: 0.1%, 8.4%) of the AD outpatient visits were attributed to

299   high temperature (Table 3).

300

301   **Sensitivity analysis**

302   In the above model, after changing the dfs of the spline functions for relative humidity, sunshine

303   duration, atmospheric pressure, precipitation and time trend, and different numbers of maximum

304   lag days for temperature, the total AFs remained statistically significant and consistent with the

305   results described above, which indicated the robustness of the analysis (Tables S2-S3). We

306   adjusted other covariates (SO_2 or NO_2), and the main results did not change significantly (Tables

307   S4). In addition, the result of the model based on the optimal BIC was very similar to the model

308   based on the optimal AIC, which led to no change in the model selection.

309

310   ## Discussion

311   This is the first time-series study to investigate the association between ambient temperature and

312   AD morbidity, and estimate the temperature-attributable burden of AD in China. Our study

313   found that nearly one-quarter of the AD outpatient visits were attributed to temperature. Both

314   high and low temperatures could increase the risk of AD, with a more pronounced increase at

315   low temperatures. According to the subgroup analysis, children and males were found to be the

316   population that were most susceptible to extreme temperatures. We demonstrated, for the first

317   time, that the optimum temperature for the lowest AD morbidity ranged from 19.6-25.3 °C.

318

319   It is evident that weather conditions have significant impacts on AD morbidity, which is not

320   surprising given that the skin is the organ most directly exposed to the external environment

321   (*Gravitz,2018*). However, the relative contributions of cold and hot weather to AD as well as

322   other dermatological conditions remain poorly defined. Consistent with a report from the United

323   States of America (*Fleischer,2019*), we found that both hot and cold temperatures were

324   associated with an increase in AD visits. These findings are in contrast to other studies that

325   showed that only cold or hot weather is associated with AD (*Fleischer,2019; Ibekwe &*

326   *Ukonu,2019; Silverberg et al.,2013; Vocks et al.,2001*). The reasons for this discrepancy are

327   unclear and may be due to the varying adaptability of people to unique meteorological conditions

328   in different regions. Alternatively, the discrepancy may be related to the application of different

329   analysis methods or different criteria to define cold and hot weather. If a linear model were

330   applied, it would only identify either a positive or negative association, without taking into

331   account more complicated effects.

332

333   In the present study, a U-shaped temperature-AD relationship was observed, and low

334   temperatures were related to an increased risk of AD. This is consistent with studies from the

335   USA in which AD outpatient visits increased as air temperature decreased, peaking in the winter

336   (*Fleischer,2019; Silverberg et al.,2013*). Clinical investigations have suggested that low

337   temperatures could promote proinflammatory cytokine and mast cell reactivity within the skin,

338   which is highly correlated with AD inflammation (*Engebretsen et al.,2016*). Additionally, cold

339   temperature can activate transient receptor potential ankyrin 1 (TRPA1) on the surface of

340   keratinocytes and increase the influx of calcium ions into epidermal keratinocytes (*Denda et*

341   *al.,2003; Denda et al.,2007*). Consequently, this process undermines the epidermal barrier and

342   slows down its recovery, thereby decreasing the permeability of the barrier and increasing the

343   trans-epidermal water loss (TEWL), stimulating or exacerbating AD (*Maglie et al.,2021*).

344

345   In addition, our study showed that hot temperatures were also associated with an increased risk

346   of AD. This observation is consistent with previous studies from the USA and Shanghai, China

347   (*Fleischer,2019; Li et al.,2016; Wang et al.,2021*). One possible explanation is that when the

348   weather becomes warmer, people tend to produce more perspiration. The acidity of perspiration

349   could have an irritant effect on the skin and contribute to Th-2 inflammation (*Ständer &*

350   *Steinhoff,2002*). Malassezia has also been found in perspiration residue on the skin surface and

351   has been reported to be positively associated with AD (*Hiragun et al.,2013*). Moreover,

352   myelinated (Aδ) and unmyelinated (C) nerve fibers are reported to be more active in

353   environments with high temperatures and could lead to itching, which is a typical symptom of

354   AD (*Dawn et al.,2009; McGlone & Reilly,2010*).

355

356   Diverse demographic characteristics might contribute to the modification effects of temperature

357   on AD outpatient visits. A study from Korea found that children with AD are likely to have

358   heavier symptoms in spring, autumn, and winter (*Kim et al.,2017*). Children's filaggrin levels are

359   usually lower, with greater epidermal hyperplasia (*Nygaard et al.,2016*). As demonstrated in a

360   proteomic study, the downstream mechanisms of lower filaggrin levels are likely to involve a

361   dysregulation of multiple other proteins relevant to inflammatory, proteolytical and cytoskeletal

362   functions (*Elias et al.,2017*). Moreover, compared with adults, children express higher levels of

363   T helper 17 cell (Th-17) related cytokines, IL-31, IL-33 and antimicrobial peptides, which are

364   crucial substances in the pathogenesis of AD (*Nygaard et al.,2016*). Our finding of a greater

365   number of AD cases among children in this study (24.7% among children under 7 years old)

366 supports the vulnerability of children when exposed to temperatures, and urges the necessity of

367 passive primary prevention for children (*Guo et al.,2016*). Our study also suggests that males are

368 more susceptible to temperature exposure than females. It has been reported that sex hormones

369 may have multiple roles in AD, including immune responses, skin barriers and pruritus (*Kanda*

370 *et al.,2019*). For example, the dehydroepiandrosterone and testosterone levels in male patients

371 with AD were significantly lower than those in controls (*Tabata et al.,1997*). Lower levels of

372 these two substances could undermine the inhibitory effect of Th-2 cells, thus leading to an

373 increase in the risk of AD (*Pace et al.,2017*). In addition, the hydration function of females is

374 stronger, resulting in lower TEWL compared with males (*Pace et al.,2017*).

375

376 In this study, we found the optimal temperature range to be 19.6-25.3°C, which provides

377 evidence for preventing AD in cities with similar climate conditions to Chengdu. However, one

378 study focusing on temperature effects on AD in Beijing of China showed a wider range of

379 suitable temperatures while no significant effect was observed with heat (*Guo et al.,2019*). These

380 findings suggest that the temperature-health relationships and optimal temperature ranges may

381 vary in different regions, due to different climatic, geographic and socioeconomic conditions

382 (*Chen et al.,2018*). Clearly, more research on the effect of AD based on local climate conditions

383 is needed, and different cities or regions should develop unique and suitable risk-response

384 strategies in the future. In addition, we found the cold temperature effects last for 7-8 days and

385 the hot temperature effects last for 3-4 days. The Finding showed that cold has longer lasting

386 health effects on the population than heat, and the evidence is particularly important for the

387 development of specific measures to protect vulnerable populations.

388

389 The exposure-response relationship between temperature and AD has typically been estimated

390 based on ratio measures (e.g., RR or OR) in previous studies. It is true that these measures are

391 practical for quantifying exposure-response associations, but they do not provide a

392   comprehensive picture of the true impact of exposure. Attribution analysis is more useful for

393   planning and evaluating public health interventions, as it quantifies the actual burden of exposure

394   on population health. As another contribution, we determined that for the first time,

395   approximately 1/4 of AD outpatient visits were attributed to extreme temperatures in Chengdu,

396   which indicates that AD is a temperature-sensitive disease that needs to be brought to the

397   attention of policymakers, clinicians, and the public at large.

398

399   China is one of the largest countries susceptible to climate change worldwide, and the frequency

400   and intensity of extreme weather events are expected to increase (*Cai et al.,2021*). These

401   deteriorating climatic conditions may contribute to a higher number of AD patients. Strategies

402   based on these results could be proposed and developed to mitigate the effects of climate change.

403   For instance, dermatologists should educate vulnerable populations to improve their self-

404   protection awareness, and take protective measures for extreme cold or hot conditions, such as

405   installing air conditioners and avoid outdoor activities on extreme weather days.

406

407   Several limitations of this study should be acknowledged. First, it was performed in only one

408   area in China with a subtropical monsoon climate and a relatively high AD morbidity, so it is

409   unclear whether our findings can be generalized to other areas in China or other countries with

410   different climate characteristics. Second, for a small fraction of the AD outpatient visits in this

411   study we were unable to differentiate whether they were new patients or follow-up patients with

412   AD, or to track their lifestyles and work environments. Third, this is an ecological study focusing

413   on the association between temperature and AD, but it did not prove causality. Last, this study

414   was based on a single center, so selection bias might exist despite the relatively good

415   representativeness of West China Hospital due to its large number of patient visits.

416

417   **Conclusions**

418 In conclusion, our results suggest that AD is extremely sensitive to climatic conditions, with a

419 high proportion of AD occurrences attributed to temperature. Both low and high temperatures

420 could increase the risk of AD, and cold temperatures have more significant effects. Males and

421 children were the populations most affected by temperature. Given the increasingly intensified

422 global climate change, more comprehensive estimates of the impact of extreme temperature on

423 AD development and health care are required to improve awareness, prevention and

424 management.

425

426 **References**

427

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584

Figure 1

Figure 1 Distribution of the monthly averaged daily mean temperature and the number of AD outpatient visits between 2015 and 2020 in Chengdu, China.

The black solid line shows the distribution of monthly averaged daily mean temperature, and the black dotted line indicates the number of daily mean outpatients in each month.

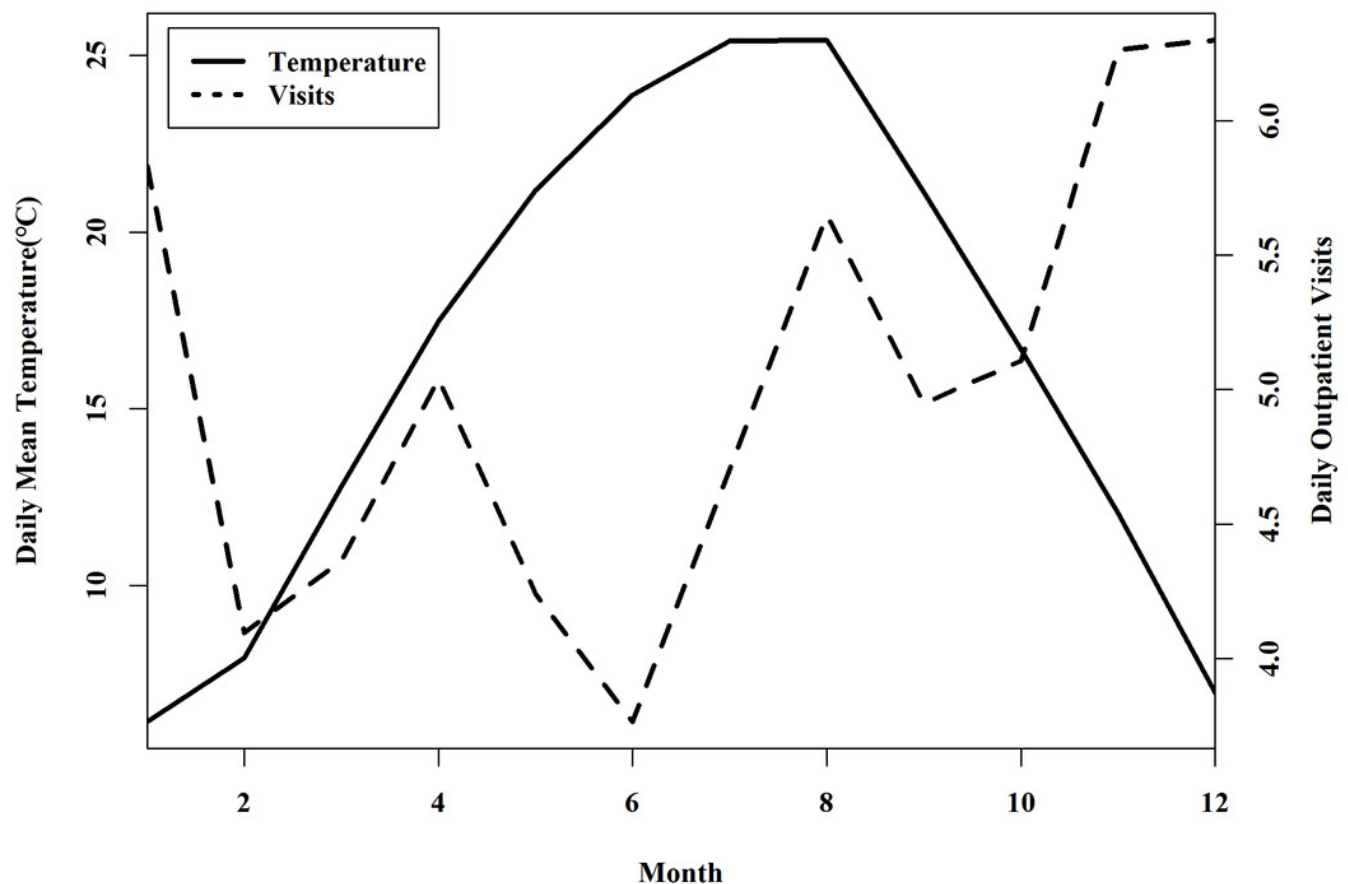



Figure 2

Figure 2 Overall cumulative association between daily mean temperature and the number of AD outpatient visits in Chengdu, China.

RR, risk ratio; Freq, frequency of AD outpatient visits. The solid red curve shows the estimated RR at different temperatures. The grey area indicates the 95% confidence intervals. The vertical dotted line indicates the minimum mortality temperature (MMT). The two vertical dashed lines represent the 1st and 99th percentiles of the distribution of daily mean temperature as shown at the bottom.

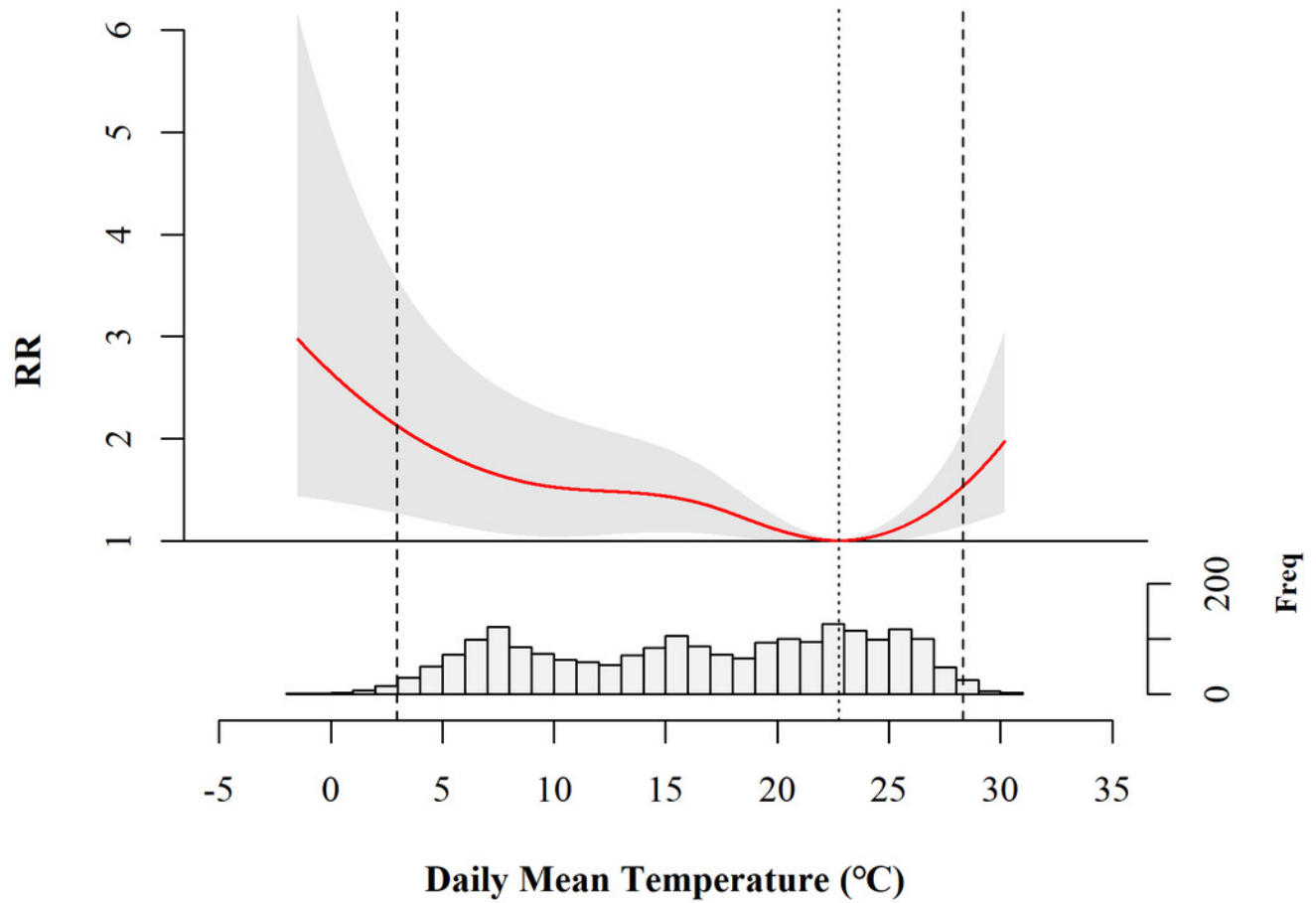
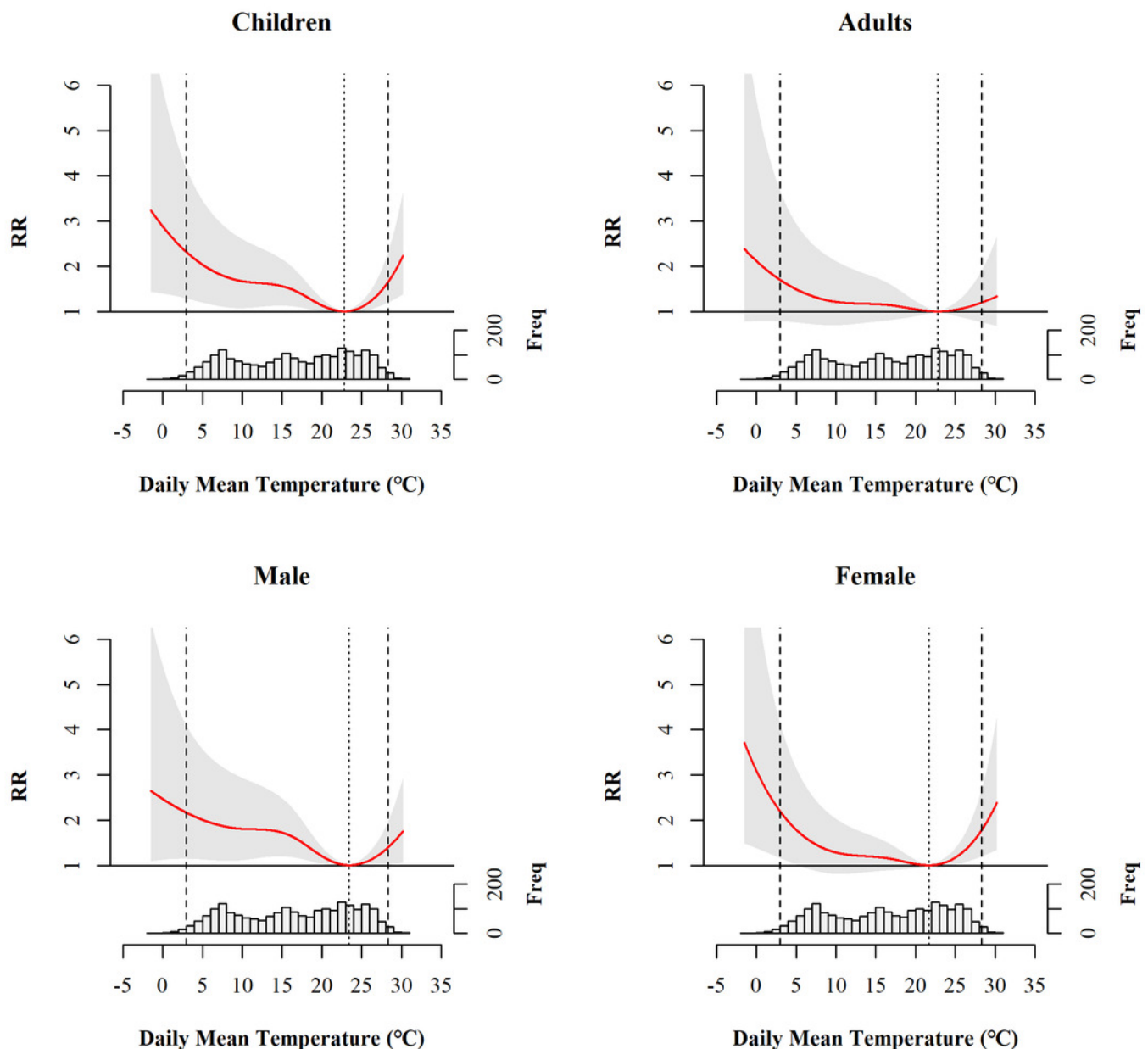



Figure 3

Figure 3 Overall cumulative association between daily mean temperature and the number of AD outpatient visits in different patient groups.

Ta ble 1. Summary statistics of AD outpatient visits, meteorological indicators and air pollutants between 2015 to 2020 in Chengdu, China.

Abbreviations: Temp, temperature; RH, relative humidity; SH, sunshine duration; SP, surface air pressure; TP, total precipitation. $PM_{2.5}$, particulate matter that has a diameter of fewer than 2.5 micrometers; NO_2, nitrogen dioxide; SO_2 sulfur dioxide. SD, standard deviation; P_{25}, the first quartile; P_{50}, the second quartile (median); P_{75}, the third quartile; Min, minimal value; Max, maximal value.

1 **Table 1.** Summary statistics of AD outpatient visits, meteorological indicators and air pollutants

2 between 2015 to 2020 in Chengdu, China.

Variable	Mean	SD	Min	P_{25}	P50	P75	Max
AD cases							
All cases	5.0	5.1	1.0	1.0	4.0	8.0	58.0
Age (years)							
≤18	3.6	3.9	1.0	1.0	3.0	6.0	46.0
>18	1.4	1.9	0.0	1.0	1.4	2.0	14.0
Sex							
Male	2.9	3.1	1.0	1.0	2.0	4.0	38.0
Female	2.1	2.5	0.0	0.0	1.0	3.0	26.0
Meteorology							
Temp (℃)	16.5	7.3	-1.5	9.7	17.0	22.9	30.2
RH (%)	81.0	9.8	40.5	74.8	82.2	88.5	99.1
SH (h)	2.7	3.3	0.0	0.0	1.2	5.0	12.3
SP (kpa)	92.6	0.7	91.0	92.0	92.7	93.2	94.3
TP (mm)	3.0	6.0	0.0	0.3	1.2	3.1	95.4
Air pollution							
$PM_{2.5}$ (μg/m³)	48.1	31.8	6.1	25.8	39.9	60.9	270.4
NO_2 (μg/m³)	41.2	14.4	7.6	30.6	39.8	49.9	105.0
SO_2 (μg/m³)	11.0	5.3	3.8	7.0	9.5	13.5	38.7

3 Abbreviations: Temp, temperature; RH, relative humidity; SH, sunshine duration; SP, surface air

4 pressure; TP, total precipitation. $PM_{2.5}$, particulate matter that has a diameter of fewer than 2.5

5 micrometers; NO_2, nitrogen dioxide; SO_2 sulfur dioxide.

6 SD, standard deviation; P_{25}, the first quartile; P_{50}, the second quartile (median); P_{75}, the third

7 quartile; Min, minimal value; Max, maximal value.

Table 2. The total health burden of AD outpatient's visits attributed to extreme temperatures from 2015 to 2020 in Chengdu, China.

AF, attributable fraction; AN, attributable number. Bolded numbers and confidence intervals indicate statistical significance.

1 **Table 2.** The total health burden of AD outpatient's visits attributed to extreme temperatures
2 from 2015 to 2020 in Chengdu, China.

Variables	AF (%, 95% eCI)	AN (n, 95% eCI)
Total	**25.4 (9.2, 36.0)**	**2724.4 (955.7, 3909.2)**
High temperature	**3.0 (0.5, 5.0)**	**322.1 (45.9, 538.7)**
Low temperature	**22.4 (5.3, 34.1)**	**2403.4 (698.2, 3744.1)**

3 AF, attributable fraction; AN, attributable number.
4 Bolded numbers and confidence intervals indicate statistical significance.

Table 3. The health burden of AD outpatient's visits attributed to extreme temperatures for each subgroup from 2015 to 2020 in Chengdu, China.

AF (%, 95% eCI), attributable fraction; AN ((n, 95% eCI), attributable number. Bolded numbers and confidence intervals indicate statistical significance.

2 **Table 3.** The health burden of AD outpatient's visits attributed to extreme temperatures for each

3 subgroup from 2015 to 2020 in Chengdu, China.

Variables	Total		High temperature		Low temperature	
	AF	AN	AF	AN	AF	AN
Age						
Children	**29.3**	**2291.1**	**3.6**	**279.9**	**25.8**	**2012.3**
	(11.5, 40.6)	**(884.0,3220.9)**	**(0.6,6.1)**	**(73.6,453.8)**	**(8.9,38.0)**	**(505.1,2952.6)**
Adults	13.4	395.8	1.2 (-	34.8	12.2	361.1 (-
	(-13.3,29.8)	(-411.3,922.5)	3.6,4.6)	(-100.8,147.8)	(-17.0,30.9)	541.7,903.2)
Sex						
Male	**30.8**	**1885.3**	2.1	126.2	**28.7**	**1759.7**
	(11.6,43.6)	**(673.2,2673.6)**	(-0.7,4.2)	(-39.8,263.4)	**(9.1,41.3)**	**(618.9,2592.2)**
Female	20.1	929.5	**4.7**	**219.6**	15.3	710.1
	(-1.9,32.1)	(-51.2,1575,2)	**(0.1,8.4)**	**(9.1,386.0)**	(-5.4,27.9)	(-128.1,1312.8)

4 AF (%, 95% eCI), attributable fraction; AN ((n, 95% eCI), attributable number.

5 Bolded numbers and confidence intervals indicate statistical significance.