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Synergistic associations of ambient air pollution and heat on daily mortality in India

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**1 Synergistic associations of ambient air pollution and heat on daily mortality in India**

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50 **Highlights:**

- 51 • Unique multi-city study evaluating the interaction between air pollution and heat in India.
- 52 • We used two advanced spatiotemporal models to estimate daily exposure levels.
- 53 • We observed substantial synergistic interaction between air pollution and heat in India.
- 54 • Heat-related mortality was 1.5 times higher at the most extreme PM<sub>2.5</sub> levels.
- 55 • Efforts to reduce common sources of air pollution and climate change to lower daily mortality.

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77 **Abstract:**

78 **Background:** Limited studies have evaluated the interaction between ambient air pollution and heat on  
79 mortality, especially in regions such as India, where extreme levels of both exposures occur frequently.  
80 Accordingly, we aimed to investigate the potential synergistic effects between ambient air pollution and  
81 heat on daily mortality in India.

82 **Methods:** We applied a time-series analysis for ten cities in India between 2008-2019. We assessed  
83 city-wide daily particulate matter  $\leq 2.5\mu\text{m}$  ( $\text{PM}_{2.5}$ ) and temperature levels using two nationwide  
84 spatiotemporal models. We estimated city-specific exposure-outcome associations through generalised  
85 additive Poisson regression models, and meta-analysed the associations. To evaluate the interaction  
86 between  $\text{PM}_{2.5}$  and air temperature (modelled at lag 0–1), a product term was incorporated between  
87 linear  $\text{PM}_{2.5}$  and non-linear air temperature. From this model, we estimated the effect of air pollution  
88 for increasing levels of temperature, and vice versa.

89 **Findings:** Among ~3.6 million deaths, we found that the association of  $\text{PM}_{2.5}$  on mortality was  
90 particularly stronger beyond the 75<sup>th</sup> percentile of temperature. When we compared the associations of  
91  $\text{PM}_{2.5}$ -mortality at the 75<sup>th</sup> and 99<sup>th</sup> temperature percentile, we observed an increase from 0.8% (95%  
92 CI: -0.3%, 1.9%) to 4.6% (95% CI: 2.9%, 6.5%) increase in mortality per 10  $\mu\text{g}/\text{m}^3$  increments,  
93 respectively. In addition, we observed a 22.0% (95% CI: 13.5%, 31.2%) increase in daily mortality risk  
94 due to an increase in temperature from the 75<sup>th</sup> to the 99<sup>th</sup> city-specific percentiles. Percent change in  
95 mortality risk increased linearly from 8.3% (95% CI: 2.2%, 14.9%) when daily  $\text{PM}_{2.5}$  was 20  $\mu\text{g}/\text{m}^3$  to  
96 63.9% (95% CI: 38.7%, 93.7%) at 100  $\mu\text{g}/\text{m}^3$ .

97 **Interpretation:** Our findings reveal a substantial synergistic interaction between ambient air pollution and  
98 temperature in India. This calls for efforts to tangibly reduce common sources of air pollution and

99 climate change to immediately lower their combined effects on daily mortality and mitigate their long-  
 100 term health consequences.

101 **Key words:** India, ambient air pollution, heat, interaction, climate change.

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## 111 1. Introduction

112 Climate change is considered the biggest health threat facing humanity, as stated by the World Health  
 113 Organization (World Health Organization, 2021). Climate change can affect human health through  
 114 multiple exposure pathways such as extreme weather events (e.g. floods, droughts), increased disease  
 115 vectors, and ambient air pollution and extreme temperatures, among many others (Romanello et al.,  
 116 2023). Among these, extreme temperatures have been identified as the most important factor in weather-  
 117 related deaths globally (Abbasati et al., 2020; Ebi et al., 2021). Particulate matter air pollution (both  
 118 indoor and ambient) has an even larger public health impact and is considered the leading contributor  
 119 to the Global Burden of Disease, leading to 8.0% of the total disability-adjusted life-years (DALYs)  
 120 (Brauer et al., 2024). People in south Asia, sub-Saharan Africa, and parts of north Africa and the Middle  
 121 East at greatest risk (Brauer et al., 2024; Health Effects Institute, 2024). Clearly both air pollution and  
 122 high temperature individually represent public health threats but studies evaluating interactive effects  
 123 between these two environmental factors are limited, potentially underestimating their joint health  
 124 effects and mitigation opportunities (Anenberg et al., 2020).

125 Pointedly, the combustion of fossil fuels is a source of both air pollution and greenhouse gases, the  
 126 latter of which contribute to both climate change and are the target of climate mitigation strategies. By  
 127 reducing fossil fuel combustion for energy production, these strategies will also concurrently decrease  
 128 air pollution (Keswani et al., 2022). This dual benefit will help in reducing the health effects of both  
 129 climate change and ambient air pollution (Keswani et al., 2022). The need to mitigate the effects of  
 130 climate change is especially critical in India, where temperatures have been rising over the past decades,  
 131 and a majority of the population is exposed to extreme levels (Mazdiyasni et al., 2017).

132 To date, the potential synergistic effects of extreme air pollution and high temperature on health remain  
 133 inconclusive (Anenberg et al., 2020; Cheng et al., 2024; Hu et al., 2022; Rai et al., 2023; Stafoggia et  
 134 al., 2023; Zafeiratou et al., 2024). A review found that 48% of the included studies identified an  
 135 interaction between air pollution and heat on various health outcomes (Anenberg et al., 2020). Most  
 136 studies have mainly explored if one exposure modified the other exposure-mortality relationship, such  
 137 as a recent meta-analysis that did not establish that particulate matter  $\leq 2.5\mu\text{m}$  ( $\text{PM}_{2.5}$ ) modified  
 138 temperature-related mortality (Hu et al., 2022; Li et al., 2017). The most comprehensive study so far  
 139 included 620 cities across 36 countries and, in contrast, suggested an interaction between air

140 temperature and air pollution on daily mortality (Stafoggia et al., 2023). Nevertheless, comparing these  
 141 studies is challenging due to the heterogeneous methodologies used to evaluate the interaction between  
 142 both exposures, and the limited data available from low- and middle-income countries (LMICs) such  
 143 as India. This is important because the intersection of high concentrations of ambient air pollution and  
 144 extremes of heat are more likely to occur in LMICs situated in the global south. Furthermore,  
 145 understanding the health implications of co-occurring environmental extremes can inform more  
 146 targeted strategies for policymakers and healthcare professionals to manage the combined impacts of  
 147 both exposures.

148 Our objective was to carry out a comprehensive analysis across multiple Indian cities, using two  
 149 national spatiotemporal exposure models to estimate daily air pollution and temperature levels. We used  
 150 a distinctive dataset of daily mortality levels from ten different cities in India. Our specific aim was to  
 151 investigate the synergistic effect between ambient air pollution and heat on daily mortality in India.

## 152 2. Methods

### 153 2.1. Daily mortality data collection

154 We collected daily counts of all-cause mortality from the death registries of 10 city municipal  
 155 corporations in India, spanning various climate zone classifications from arid to tropical monsoon and  
 156 temperate climates. The included cities were Ahmedabad, Bangalore, Chennai, Delhi, Hyderabad,  
 157 Kolkata, Mumbai, Pune, Shimla, and Varanasi. The period of data collection extended from 2008 to  
 158 2019, with varying length of available data for each city, from 3 to 9 years. The selection of these 10  
 159 cities was based on data availability and the feasibility of collaboration. In the absence of International  
 160 Classification of Diseases (ICD) codes for most cities to estimate cause-specific mortality, we cleaned  
 161 and aggregated the de-identified mortality records obtained from the municipalities to estimate daily  
 162 counts of all-cause mortality for each municipal corporation.

### 163 2.2. Exposure assessment

164 We generated daily average PM<sub>2.5</sub> concentrations and mean temperature at 1 km x 1 km spatial  
 165 resolution across India using two separate hybrid ensemble averaging approaches (temperature model  
 166 currently under review) (Mandal et al., 2024). Briefly, we collected ground monitoring-based  
 167 observations of daily average PM<sub>2.5</sub> and PM<sub>10</sub> across 1056 locations as well as 650 temperature stations  
 168 and an extensive set of predictors including satellite-based observations, meteorology, land-use  
 169 patterns, emissions inventories, and reanalysis-based data. We trained our models using four machine  
 170 learning methods (deep learning, random forests, gradient boosting, and extreme gradient boosting) on  
 171 the training data (80% of the available monitors) for both the air pollution and temperature model  
 172 (Mandal et al., 2024). The temperature model additionally used Extreme Random Forests as a predictor  
 173 model. The optimised models were implemented on the left-out validation data (20% of the monitors)  
 174 to obtain learner-specific predictions and combined using a Gaussian process regression for the PM  
 175 model and a Gradient Boosting method for the temperature model as well as to obtain the final  
 176 predictions. This methodology allowed us to obtain PM<sub>2.5</sub> and temperature exposures in regions with  
 177 no monitoring data across time as well as variances across different land spaces. The daily ensemble  
 178 averaged predictions for PM<sub>2.5</sub> had a cross-validated R<sup>2</sup> of 86% and mean absolute error ranging  
 179 between 14.1 - 25.4 µg/m<sup>3</sup> across India. The daily ensemble averaged predictions for temperature had  
 180 a cross-validated robust R<sup>2</sup> of 93% and mean absolute error ranging between 0.9 - 1.4 °C across the  
 181 country. In this study, we estimated daily population weighted air pollution and temperature levels  
 182 including all 1km x 1km grid cells contained within the boundaries of each of the 10 municipal  
 183 boundaries included in the study.

### 184 2.3. Statistical analysis

### 185 Individual associations of air pollution and heat

We previously published the individual effect of PM<sub>2.5</sub> using the method described subsequently and have included it here to facilitate interpretation and comparison to the interaction effect (de Bont et al., 2024). We applied a two-step analytical framework to evaluate the associations of PM<sub>2.5</sub> and temperature with daily mortality. We first estimated city-specific associations and subsequently performed a meta-analysis of these associations in the second step. We applied a quasi-Poisson generalised additive model to evaluate the city-specific associations. These models were adjusted for several time-varying covariates, including a penalised spline function of calendar day (nine degrees of freedom[*df*] per year) to accommodate long-term and seasonal trends, and a day-of-week indicator to address weekly variations. For air pollution estimates we additionally adjusted for temperature as prior literature has indicated that temperature is an important confounder of air pollution - mortality relationships, while the inverse (air pollution as a confounder of temperature) is less clear (Hu et al., 2022; Li et al., 2017). For both PM<sub>2.5</sub> and air temperature, we modelled the average level of the current and previous day (lag 0-1), which is the most commonly used lag in the literature on acute air pollution and heat effects on mortality (A et al., 2015; Liu et al., 2019; Stafoggia et al., 2023). We conducted separate analyses for each exposure, considering a linear association for PM<sub>2.5</sub> and a nonlinear association for temperature, modelling temperature with a natural spline with 4 degrees of freedom (4df). The effect estimates were expressed as percentage change in daily mortality per 10 µg/m<sup>3</sup> increase for PM<sub>2.5</sub> and for heat for an increase in mean temperature from 75<sup>th</sup> to 99<sup>th</sup> of the city-specific distributions. In the second step, a random-effects meta-analytical model was employed to aggregate the city-specific estimates of associations between PM<sub>2.5</sub> and heat with mortality. I<sup>2</sup> statistics and Cochran's Q-test were computed to assess between-city heterogeneity.

## Interaction between air pollution and heat

The two-step analytical framework was also applied to evaluate the interaction between air pollution and heat. To do so, we added an interaction term between air pollution (lag 0-1) modelled as a linear term and air temperature (lag 0-1) modelled as nonlinear term by adding a natural spline (Stafoggia et al., 2023). We defined 'interaction' on a multiplicative scale as the deviation from the expected combined effect of air pollution and heat on mortality if they were acting independently. By adding an interaction between a spline and a linear term, we obtain a 3-d curve presenting relative risks at all combinations of PM concentrations and temperature percentiles. Hence, the interaction term allows us to extrapolate the change in mortality per 10 µg/m<sup>3</sup> increase of PM<sub>2.5</sub> from the 1<sup>st</sup> to the 99<sup>th</sup> air temperature percentiles of each city distribution. We additionally were able to extrapolate the percent change in mortality due to the increase in mean temperature from the 75<sup>th</sup> to 99<sup>th</sup> percentile, corresponding to an increase of daily average concentration of PM<sub>2.5</sub> from 20 µg/m<sup>3</sup> until 100 µg/m<sup>3</sup>. The selection of these predefined PM<sub>2.5</sub> ranges was guided by an examination of city-specific air pollutant distributions at different temperature percentiles. We did not observe sufficient observations below 20 µg/m<sup>3</sup> and above 100 µg/m<sup>3</sup> (Figure S1). In general, as temperatures increase, PM<sub>2.5</sub> levels typically fall as convective currents collect and disperse local pockets of high pollution into the upper atmosphere away from measurement and inhalation (Li et al., 2015; Yang et al., 2017). In our data, some cities reached their peak pollution levels, around 100 µg/m<sup>3</sup>, during the hottest days (Figure S1). However, there were some cities that exceeded this pollution level, but only during significantly colder days when PM<sub>2.5</sub> was less dispersed (Liu et al., 2020). We further evaluated the p-value for interaction by extracting the interaction terms (beta estimates) from the interaction model for each city. We then meta-analysed these estimates and applied a Wald test to determine statistical significance of the interaction. To visualise the interaction between air pollution and temperature for each city, we showed three-dimensional surfaces by applying thin-plate splines (Wood, 2003).

## Sensitivity analyses

We conducted multiple sensitivity analyses to assess consistency of our findings. First, to evaluate the robustness of our adjustments for time trends, we applied different *df/year* from 6 to 10*df/year* compared to 9 from our main analyses. Second, we evaluated different lag patterns including a 4-day moving average (lag 0-3) for both exposures, and for temperature we additionally evaluated a 11-day moving average (lag 0-10), in order to capture delayed effects of heat. In addition, we applied a lag structure

237 using a DLNM model using the same lag patterns instead of the moving average to validate our primary  
 238 lag approach. Third, we focused on the hottest period of the year as our analysis was focused on heat,  
 239 by restricting our analyses to the four consecutive hottest months for each city (models were adjusted  
 240 including a penalised spline smooth with  $3df/year$  and a day-of-week indicator). We selected four  
 241 months to capture only the summer season and to avoid overlap with the monsoon period.

### 242 3. Results

243 In these 10 cities in India, over 3.6 million deaths occurred from 2008 to 2019. The average daily  $PM_{2.5}$   
 244 levels were the highest in Delhi ( $113 \mu g/m^3$ ) and Varanasi ( $82 \mu g/m^3$ ), while the lowest in Shimla ( $28$   
 245  $\mu g/m^3$ ) (Table 1). On days when the temperature exceeded the 75<sup>th</sup> percentile, cities such as Ahmedabad,  
 246 Mumbai, and Shimla experienced higher daily mean  $PM_{2.5}$  levels compared to the annual daily mean.  
 247 Conversely, mean  $PM_{2.5}$  levels were lower in Delhi, Kolkata, and Varanasi during the warmest days,  
 248 but showed higher levels during the coldest days (Figure S1). Daily mean temperatures were the highest  
 249 in Chennai ( $32.4 ^\circ C$ ) and the lowest in Shimla ( $15.6 ^\circ C$ ). In line with the air pollution levels, cities such  
 250 as Ahmedabad, Mumbai, and Shimla had higher mean temperatures during extreme air pollution events  
 251 (above the 75<sup>th</sup> percentile). In contrast, in Delhi, Kolkata, and Varanasi, the mean temperature was lower  
 252 during these high pollution events.

253 **Table 1:** descriptive of the study population.

City	Time period	Daily deaths, mean (SD)	$PM_{2.5}$	$PM_{2.5}$ above 75 <sup>th</sup> temp,	Temperature, above 75 <sup>th</sup>	
			mean $\mu g/m^3$ (SD)	mean $\mu g/m^3$ (SD)	Mean $^\circ C$ (SD)	Mean $^\circ C$ (SD)
Ahmedabad	2008 - June 2019	122 (24)	37.9 (9.7)	45.2 (13.8)	27.0 (4.8)	31.0 (3.1)
Bangalore	2008 - 2012	121 (17)	33.0 (6.5)	37.5 (4.8)	23.6 (2.1)	24.8 (2.5)
Chennai	2010 - 2019	164 (23)	33.7 (9.0)	32.4 (6.3)	28.6 (2.4)	27.0 (2.7)
Delhi	2011 - 2018	284 (44)	113.0 (64.5)	82.4 (25.9)	24.5 (7.2)	17.0 (4.8)
Hyderabad	2008 - June 2011	78 (13)	38.9 (10.4)	42.3 (7.5)	27.1 (3.6)	26.3 (4.6)
Kolkata	2010 - 2019	172 (32)	55.2 (35.3)	32.3 (9.2)	26.5 (4.3)	20.3 (2.6)
Mumbai	2009 – Nov. 2015	251 (28)	41.7 (18.5)	35.0 (12.6)	26.8 (2.3)	25.2 (2.1)
Pune	2008 - 2012	68 (11)	45.3 (22.6)	43.7 (15.6)	24.6 (3.2)	22.0 (2.5)

Shimla	2008 – Aug. 2012	4 (2)	28.4 (6.9)	31.3 (9.4)	15.6 (4.7)	17.7 (4.3)
Varanasi	2008 – Nov 2018*	22 (6)	82.1 (35.3)	63.5 (12.6)	25.9 (6.4)	18.2 (4.0)

254 \* No data was available for Varanasi in 2017

## 255 Air pollution and mortality at different temperature levels

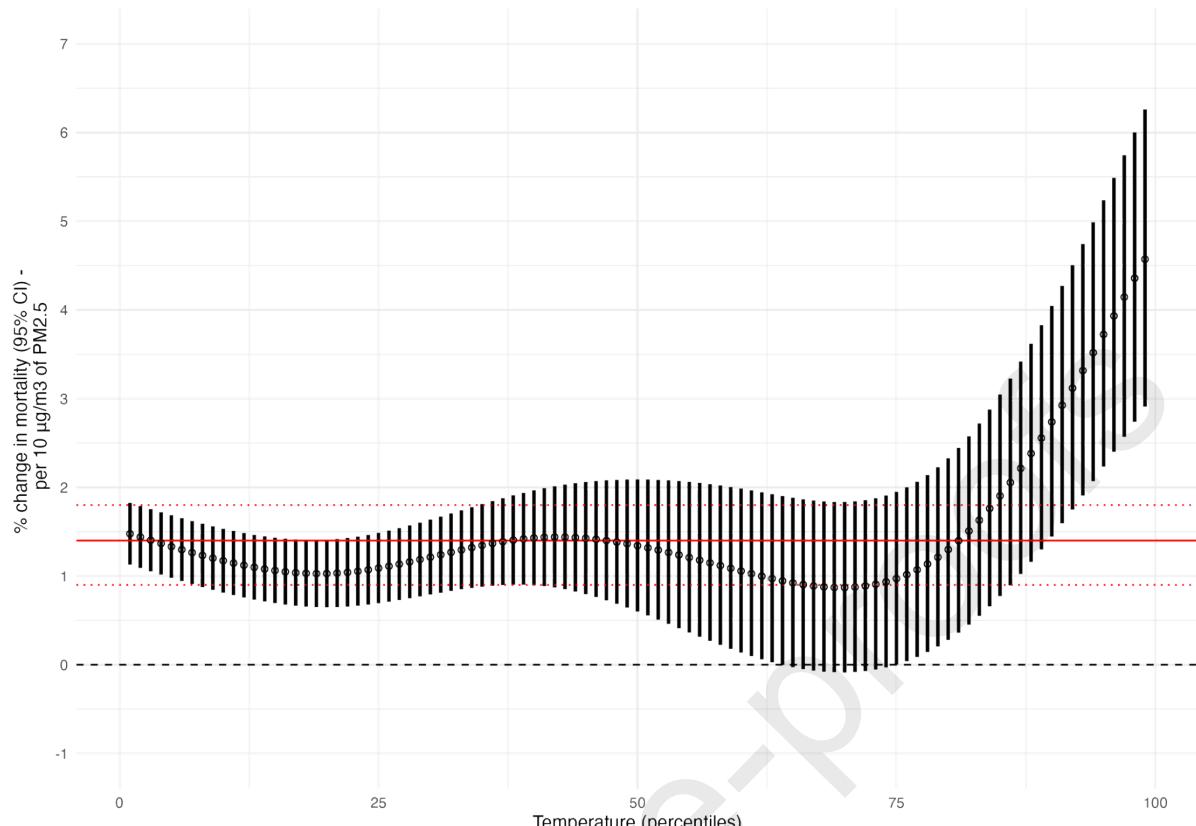
256 As in our previous publication (de Bont et al., 2024), we observed that a 10  $\mu\text{g}/\text{m}^3$  increment in PM<sub>2.5</sub>  
 257 was associated with a 1.4% (95%CI, 0.9%, 1.8%) increase in daily mortality (Figure S2). In our  
 258 interaction analysis, we found that the association of PM<sub>2.5</sub> on mortality was stronger at higher  
 259 temperature percentiles (p-value for interaction <0.001), particularly beyond the 75<sup>th</sup> percentile (Figure  
 260 1 and Table S1). Specifically, the associations of PM<sub>2.5</sub> increased from a 0.8% (95% CI: -0.3%, 1.9%)  
 261 percent change in mortality per 10  $\mu\text{g}/\text{m}^3$  increase in PM<sub>2.5</sub> when the daily temperature was at the 75<sup>th</sup>  
 262 percentile, to a 4.6% (95% CI: 2.9%, 6.5%) percent change at the 99<sup>th</sup> percentile. This increasing trend  
 263 after the 75<sup>th</sup> percentile was observed in most cities, particularly in Chennai, Delhi, and Kolkata (Figure  
 264 S3). In Varanasi, we observed an increasing trend from the 25<sup>th</sup> to the 75<sup>th</sup> percentile, which then  
 265 decreased thereafter.

## 266 Heat and mortality at different air pollution levels.

267 In our heat analyses, we observed a 22.0% (95% CI: 13.5%, 31.2%) increase in daily mortality rate due  
 268 to an increase in temperature from the 75<sup>th</sup> to the 99<sup>th</sup> city-specific percentiles. The association of  
 269 increased temperature with mortality was highest in the cities of Ahmedabad (38.1% [95% CI: 33.4%,  
 270 43.0%]) and Varanasi (60.3% [95% CI: 50.6%, 70.6%]), whereas it was lowest in Bangalore (7.1%  
 271 [95% CI: 3.4%, 11.0%]) (Figure S2). No statistically significant associations were observed in Shimla.

272 In our interaction analysis, we observed a linear increase in the association of temperature with mortality  
 273 as air pollution levels increased (p-value for interaction <0.001) (Figure 2 and table S1). Specifically,  
 274 the percent change in mortality risk due to an increase in temperature from the 75<sup>th</sup> to the 99<sup>th</sup> city-  
 275 specific percentiles increased from 8.3% (95% CI: 2.2%, 14.9%) when daily PM<sub>2.5</sub> was 20  $\mu\text{g}/\text{m}^3$  to  
 276 63.9% (95% CI: 38.7%, 93.7%) at 100  $\mu\text{g}/\text{m}^3$ . Between 24  $\mu\text{g}/\text{m}^3$  and 55  $\mu\text{g}/\text{m}^3$ , all cities contributed  
 277 to the meta-analyses, observing an increase from 11.1% (95% CI: 3.8%, 18.9%) to 29.6% (95% CI:  
 278 19.9%, 38.8%), respectively. This increasing trend was observed in most cities, particularly in  
 279 Ahmedabad, Chennai, Delhi, and Kolkata, whereas a decreasing trend was only observed in Varanasi  
 280 (Figure S4).

281 **Figure 1:** The association between air pollution (per 10  $\mu\text{g}/\text{m}^3$ ) and daily all-cause mortality across  
 282 temperature percentiles (the red line represents the % change in mortality, and the dashed lines show  
 283 the 95% CI from the non-interaction model).



284

285 Note: the effect estimates are shown in Table S1.

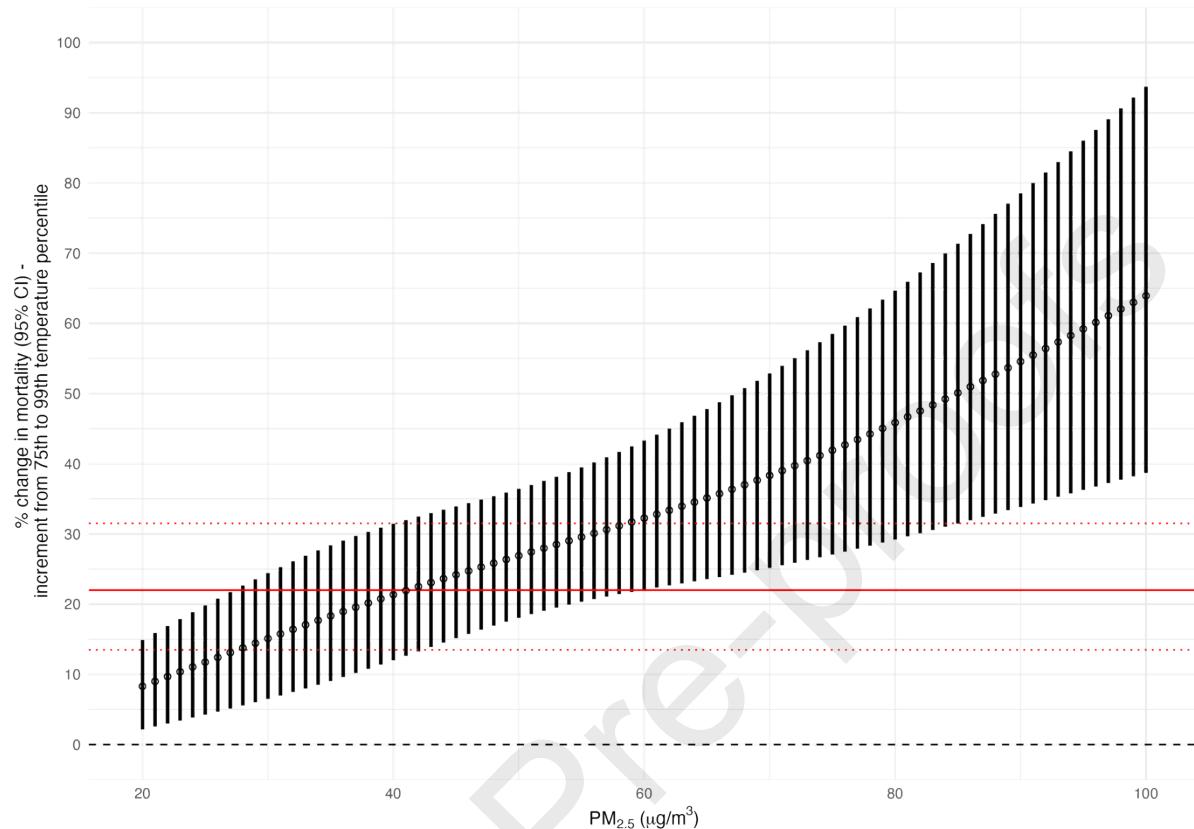
286 **Thin-plate spline regression:**

287 The results of the thin-plate spline regression for almost all cities showed higher mortality risk at higher  
 288 temperatures compared to higher air pollution levels (Figure 3). In addition, In the cities of Ahmedabad,  
 289 Bangalore, Chennai, Delhi, Kolkata, Pune and Varanasi, we observe a consistent increase of mortality  
 290 at high temperature percentiles as PM<sub>2.5</sub> levels increase from 20µg/m<sup>3</sup> to 100µg/m<sup>3</sup>. For Hyderabad,  
 291 Mumbai and Shimla, there was no clear interaction observed.

292 **Sensitivity analyses.**

293 In our sensitivity analyses for both air pollution and heat, we found similar associations when adjusting  
 294 for different time trends by varying the *df* per year (from 6 to 10 *df/year*) (Figure S5). When exploring  
 295 different lag patterns, we observed similar effect estimates using a lag of 0-3 for both air pollution and  
 296 heat. However, we did observe a reduction in the association between heat and mortality using the lag  
 297 0-10. We observed nearly identical estimates using the DLNM lag structure compared to our main  
 298 moving average approach. Further, we observed a slightly larger association when we evaluated the  
 299 increased effect of temperature from the 50<sup>th</sup>, rather than the 75<sup>th</sup> used in the main analysis, to the 99<sup>th</sup>  
 300 percentile on mortality. When we limited our analyses to the four consecutive hottest months and in  
 301 line with our main results, we found that the association of PM<sub>2.5</sub> on mortality was stronger beyond the  
 302 75<sup>th</sup> percentile of temperature Figure (S6). We further observed lower effect estimates of air pollution  
 303 below the 50th percentile of temperature during the hottest months. In addition, we observed stronger  
 304 associations between heat and mortality during the hottest months (Figure S7). The interaction effect of  
 305 air pollution on the association between heat and mortality followed a similar effect estimate until 70  
 306 µg/m<sup>3</sup> (Figure S7). After 70 µg/m<sup>3</sup>, the effect estimates were slightly lower than our main approach.

307 **Figure 2:** The association between air temperature (an increment from 75<sup>th</sup> to the 99<sup>th</sup> percentile  
 308 distribution) and all-cause mortality at different PM<sub>2.5</sub> levels (the red line represents the % change in  
 309 mortality, and the dashed lines show the 95% CI from the non-interaction model).

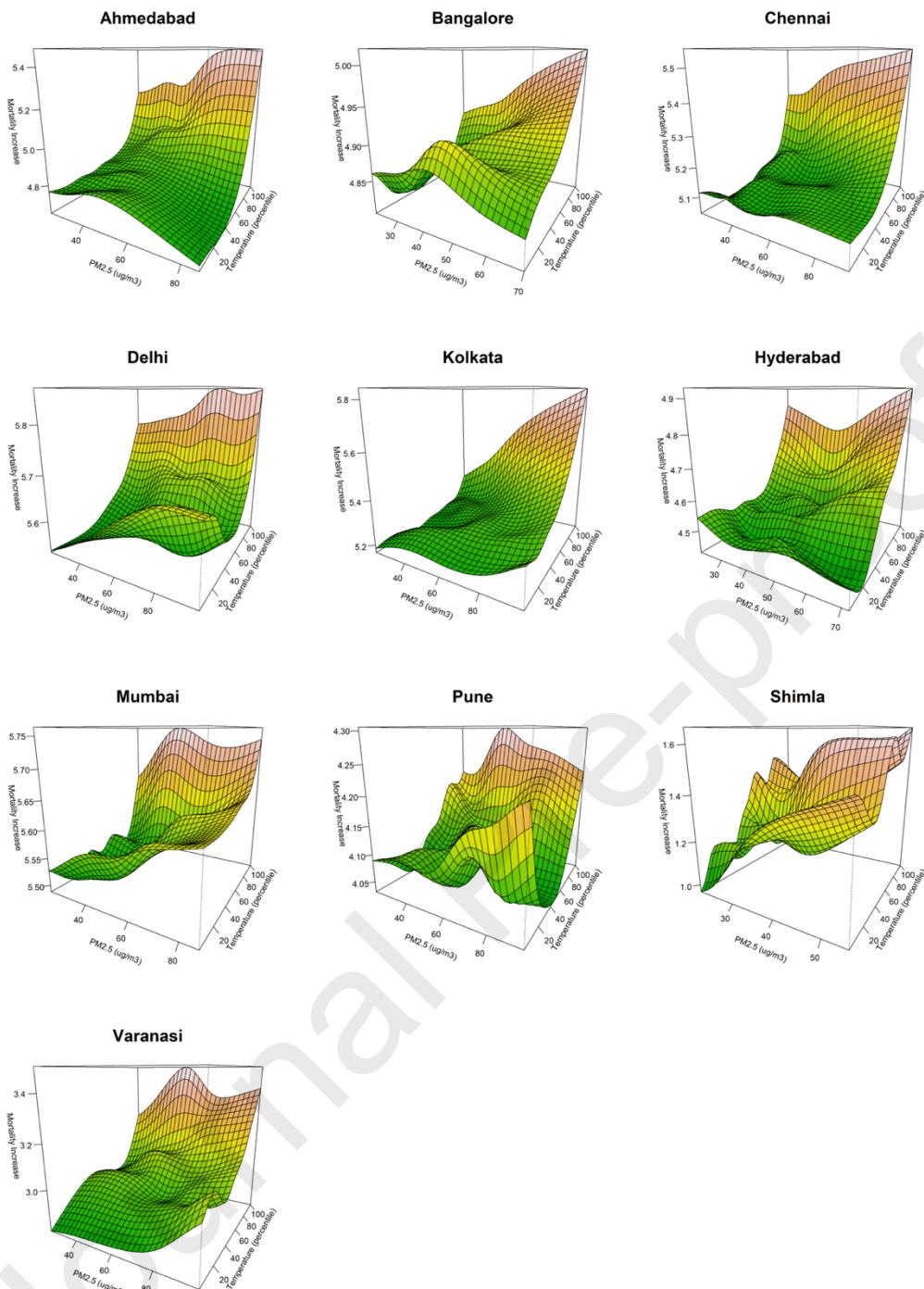


310

311 Note: the effect estimates are shown in Table S1.

312 **Figure 3:** Thin plate splines showing the synergistic interactions between PM<sub>2.5</sub> (between 20 and 100  
 313 μg/m<sup>3</sup>) and temperature (percentiles) on mortality.

314



315

316 **4. Discussion**

317 Across 10 cities in India characterised by frequent days of either extreme air pollution or high  
 318 temperatures, we observed that both PM<sub>2.5</sub> and temperature were positively associated with mortality.  
 319 We observed that the associations between PM<sub>2.5</sub> and daily mortality were more pronounced at higher  
 320 temperatures. We further found that heat-related mortality was substantially amplified with rising levels  
 321 of PM<sub>2.5</sub>, with the percent change in heat-mortality being almost 1.5 times higher at the most extreme  
 322 PM<sub>2.5</sub> levels. The synergistic associations between PM<sub>2.5</sub> and temperature on mortality were consistently  
 323 evident in three-dimensional visualisations across the different cities, highlighting the crucial  
 324 interaction between these environmental factors across India.

325 The individual associations of ambient air pollution and heat on mortality in our study are higher  
 326 compared to larger global multi-city meta-analyses studies (Liu et al., 2019; Stafoggia et al., 2023). A  
 327 comparable study including 372 cities worldwide reported a 0.4% increase in mortality for every 10  
 328  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$ , which is lower than the 1.4% increase observed in our study published  
 329 previously (de Bont et al., 2024; Stafoggia et al., 2023). Furthermore, the same study found that a  
 330 temperature increase (from the 75<sup>th</sup> to the 99<sup>th</sup> percentile) across 620 cities was associated with an 8.9%  
 331 rise in mortality, substantially lower than our observed 22% increase (Stafoggia et al., 2023). These  
 332 differences in effect size could be attributed to the extreme levels of air pollution and temperature  
 333 observed in the cities in our study, as well as variations in socio-demographic structures, vulnerable  
 334 subpopulations, air pollution composition and toxicity, and climatic differences.

335 Our study showed substantial interactions at the extreme levels of both air pollution and temperature.  
 336 Previous studies have generally reported inconclusive results, as highlighted by a meta-analysis  
 337 showing that only 19 out of 39 studies observed interactions between air pollution and heat (Anenberg  
 338 et al., 2020). Methodological differences in evaluating these interactions make direct comparisons  
 339 challenging. However, one study using a similar statistical approach, including approximately 480 cities  
 340 worldwide (excluding cities from India), reported that the associations of  $\text{PM}_{2.5}$  increased from 0.1%  
 341 per 10  $\mu\text{g}/\text{m}^3$  at the 75th percentile of temperature to 1.2% at the 99th percentile (Stafoggia et al., 2023).  
 342 In contrast, our study found a substantially higher increase in associations, ranging from 0.8% to 4.6%,  
 343 with consistently higher effect estimates across all temperature percentiles and nearly fourfold greater  
 344 effects at the highest temperature percentile. Additionally, a similar increase was observed during the  
 345 hottest months at the highest percentiles, although no effects were observed below the 50th percentile.  
 346 Results at lower percentiles should be interpreted cautiously, as temperature percentiles were calculated  
 347 for the entire year, which led to very few observations in these ranges when the dataset was restricted  
 348 to the hottest months. Future studies should explore seasonal effects in greater detail, as this was beyond  
 349 the scope of our analysis.

350 When comparing our estimates of temperature effects at different air pollution levels to those of  
 351 Stafoggia et al. (2023), their study reported that an increase in temperature (from the 75<sup>th</sup> to the 99<sup>th</sup>  
 352 percentile) resulted in an increase in mortality from 8.9% at 20  $\mu\text{g}/\text{m}^3$  of  $\text{PM}_{2.5}$  to 12.3% at 40  $\mu\text{g}/\text{m}^3$ . In  
 353 contrast, our study observed larger temperature effects, ranging from 8.3% to 21.4%, within the same  
 354 pollution range. These differences could be related to the varying absolute temperatures corresponding  
 355 to the percentiles in each study area. Moreover, our study uniquely captured a wider range of daily  
 356  $\text{PM}_{2.5}$  values, extending up to 100  $\mu\text{g}/\text{m}^3$  compared to 40  $\mu\text{g}/\text{m}^3$  in the previous study, where a  
 357 temperature increase was associated with a 63.9% change in mortality. These findings underscore the  
 358 importance of considering the potential synergies between these two exposures, as neglecting them  
 359 could lead to underestimations of the actual health burden and compromise the effectiveness of climate  
 360 change adaptation plans. We also observed some inconsistencies in the data, such as the decreasing  
 361 trend in interactive effects in Varanasi. This trend may be attributed to unique regional characteristics,  
 362 including differences in  $\text{PM}_{2.5}$  composition, local adaptation factors, or variability in baseline health  
 363 status. These aspects warrant further investigation to better understand the underlying mechanisms.

#### 364 **Biological mechanisms**

365 The pathways explaining the combined effect of air pollution and heat on mortality are still poorly  
 366 understood. Seasonal climate variation alters the patterns of air pollution composition. During the  
 367 hottest months, increased temperatures can alter the toxicity and composition of  $\text{PM}_{2.5}$ , while promoting  
 368 the formation of other pollutants such as ozone and secondary particles through chemical reactions (Im  
 369 et al., 2022; Kinney, 2008). Further, heat stress can also impact human thermoregulation mechanisms,  
 370 reducing the ability to detoxify air pollutants and increasing vulnerability due to an elevated ventilation  
 371 rate, which leads to greater intake and distribution of air pollutants (Gordon, 2003; Stafoggia et al.,  
 372 2023; Zafeiratou et al., 2024). Additionally, common pathophysiologic pathways might be activated  
 373 when exposed to both air pollution and high temperatures. Research indicates that both exposures can  
 374 increase oxidative stress, inflammatory responses, cellular damage, apoptosis, and C-reactive protein,

375 a biomarker of systemic inflammation—factors that are associated with higher mortality risk (Gordon,  
 376 Stafoggia et al., 2023; Zafeiratou et al., 2024).

### 377 Importance and public health implications

378 This study provides unique evidence of interactions at the extreme levels of both air pollution and  
 379 temperature. The escalating crisis of climate change is becoming increasingly relevant, particularly in  
 380 India and many other LMICs. These regions are not only facing rising levels of air pollution exposure,  
 381 but also experiencing more frequent, longer, and more intense heatwaves. As a result, the combined  
 382 burden of both exposures is likely to become larger. Therefore, there is an immediate need for strategies,  
 383 both short-term and long-term, to mitigate the combined effects of air pollution and climate change on  
 384 both morbidity and mortality. Actions to reduce air pollution can be implemented within a shorter time  
 385 frame than those to mitigate the impact of rising temperatures. Moreover, reducing air pollution will  
 386 also have long-term effects on climate change by decreasing carbon emissions. Given several common  
 387 pollutants for air pollution and climate change, these actions will have almost immediate effects on  
 388 reducing mortality from both air pollution and heat with co-benefits for health. Further, an important  
 389 adaptation strategy is the development of integrated surveillance and warning systems that take into  
 390 account both climate hazards and air pollution levels. When these systems define the thresholds for air  
 391 pollution and temperature extremes, it may be necessary to lower the threshold for each exposure during  
 392 days of high air pollution and temperature episodes.

### 393 394 Strength and limitations

395 This study has several strengths. Firstly, to the best of our knowledge, it is the most extensive multi-  
 396 city study conducted in India that focuses on the interaction between PM<sub>2.5</sub> and temperature in relation  
 397 to mortality. The data included over 3.6 million deaths from the most densely populated cities in India,  
 398 which experience extreme levels of air pollution (ranging from 20 to 100 µg/m<sup>3</sup>) and temperature  
 399 extremes. Secondly, we applied two advanced spatiotemporal models to estimate the daily levels of  
 400 PM<sub>2.5</sub> and temperature. This approach enabled us to go beyond the limitations of fixed site monitors and  
 401 generate population-weighted exposure metrics for each city included in the study. Lastly, we employed  
 402 a sophisticated statistical model to account for the potential nonlinear interaction between air pollution  
 403 and temperature. This approach simplified the interpretation of the interaction, facilitating our  
 404 understanding of this complex interaction.

405

406 Some limitations should be acknowledged in this study. First, there is a disparity in the quality and  
 407 completeness of death registration data across different regions in India, leading to missingness in  
 408 deaths by the civil registration system. We hypothesise that these omissions are likely random in relation  
 409 to the daily fluctuations in air pollution and temperature levels, and we expect that this is unlikely to  
 410 bias our effect estimates. Second, we estimated daily levels of PM<sub>2.5</sub> and mean temperature at the city-  
 411 level by averaging all the 1x1km gridded predictions within the boundaries of the city produced by both  
 412 of our spatiotemporal models. This spatiotemporal modelling approach is a major improvement over  
 413 previous studies that primarily relied on data from monitoring stations. However, we acknowledge that  
 414 our approach may introduce some non-differential misclassification of exposure, potentially leading to  
 415 an underestimation of our results (Zeger et al., 2000). In addition, we did not have data on individual  
 416 residential or work addresses, residential mobility, or indoor temperature and air pollution levels. This  
 417 induces exposure error, however some of that error is Berkson (e.g. individual variations around the  
 418 city average) and some is non-differential. Moreover, given that the focus of our study was on day-to-  
 419 day variability in outdoor exposures rather than fine-scale spatial contrasts, we consider these factors  
 420 to be a minor limitation with limited impact on the overall interpretation of our findings. Third, although  
 421 we included 8 of the 10 most populated cities in India, our study was limited by the lack of data from  
 422 additional cities and extended time periods, restricting generalizability to other cities, rural areas, or  
 423 time periods not covered by the data. As well, we lacked data on cause of death and vital

424 sociodemographic data such as age, sex, socioeconomic status, along with other potential individual-  
 425 level effect modifiers. We anticipate future research evaluating the interaction between air pollution  
 426 and heat might vary across different individual and contextual levels. Finally, while we were able to  
 427 estimate PM<sub>2.5</sub> at high spatial and temporal resolution, future studies should incorporate other relevant  
 428 pollutants, such as nitrogen dioxide and ozone, which may also interact with heat but were not  
 429 consistently available for all cities and for all years in our study.

430

## 431     **5. Conclusion**

432 Although it has been well-documented that daily PM<sub>2.5</sub> exposure and high ambient temperature  
 433 separately both increase day to day mortality, this study conducted in India, with both extremely high  
 434 air pollution levels and high daily temperatures, showed strong evidence of augmented mortality risk  
 435 on days with simultaneously occurring extremely high levels of daily PM<sub>2.5</sub> levels and temperature. This  
 436 is particularly concerning with the clear trend of global warming which increases the likelihood of more  
 437 high pollution-high temperature days in most cities of India and elsewhere. The imperative of reducing  
 438 PM<sub>2.5</sub> emissions and promoting and facilitating heat adaptation represents a clear opportunity to help  
 439 reduce short-term mortality from both exposures as well as justify the investment case for interventions  
 440 for both air quality management and heat adaptation. Given the common pollutants responsible for both  
 441 issues and the co-benefits for health from mitigating carbon emissions, timely and relevant programs  
 442 and policies for both air pollution and heat adaptation should be strategically pursued to improve public  
 443 and planetary health.

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456

## 457     **Contributions**

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