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Acute exposure to elevated air pollution and cause-specific mortality: A causal modeling study from 2012 to 2018 in central Indo-Gangetic Plain

Prashant Rajput[1], Rajesh Kumar Mall[1*] , Nidhi Singh[1,2] and Rajniti Prasad[1,3]

[1]*DST-Mahamana Centre of Excellence in Climate Change Research, IESD, Banaras Hindu University, Varanasi – 221 005, India*

[2]*Leibniz Research Institute for Environmental Medicine (IUF), Düsseldorf, Germany*

[3]*Institute of Medical Sciences, Banaras Hindu University, Varanasi – 221 005, India*

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***Corresponding author's email: rkmall@bhu.ac.in.**

सार – हमने भारत-गांगेय मैदान (IGP) में कारण-विशिष्ट मृत्यु दर जोखिमों पर वायु प्रदूषण (AP) के अल्पकालिक जोखिम के सीमांत प्रभाव का अनुमान लगाने के लिए तीन वायु प्रदूषकों (PM2.5, O3, and NO2), मौसम संबंधी मापदंडों और जोखिमों के संभावित अंतराल प्रभाव के साथ उलटा प्रसरण भारण (Inverse Probability Weighting - IPW) कारण मॉडलिंग को लागू किया। PM2.5 and O3 के अल्पकालिक जोखिम और मृत्यु के सभी चार मूल्यांकित कारणों (जैसे न्यूरोलॉजिकल, श्वसन, हृदय और नेफ्रोलॉजिकल मौतें) के बीच एक कारण संबंध पाया गया, जबकि NO2 का संबंध केवल हृदय मृत्यु दर जोखिमों के साथ पाया गया NO2 के जोखिम में प्रत्येक 10-ppb की वृद्धि के लिए, औसत जोखिम में 0.84% (95% विश्वास अंतराल (CI) = 0.58, 1.10) की वृद्धि हुई। अल्पकालिक PM2.5 के जोखिम में प्रत्येक 10 µg m-3 की वृद्धि के लिए, अस्पताल में होने वाली सर्व-कारण मौतों, न्यूरोलॉजिकल मौतों, श्वसन मौतों, हृदय मौतों और नेफ्रोलॉजिकल मौतों के जोखिम में क्रमशः 1.76% (1.57, 1.95), 0.28% (0.07, 0.50), 0.73% (0.47, 0.98), 0.72% (0.48, 0.96), और 0.11% (0.09, 0.14) की वृद्धि हुई। इसी तरह, PM2.5 और NO2 को नियंत्रित करने के बाद, O3 के तीव्र जोखिम और श्वसन मृत्यु दर जोखिम के बीच का कारण संबंध सभी अध्ययन किए गए परिदृश्यों में सबसे अधिक पाया गया O3 में प्रत्येक 10-ppb की वृद्धि के लिए श्वसन मृत्यु जोखिम में 2.24% की वृद्धि (2.02, 2.45) देखी गई। IPW कारण मॉडलिंग के परिणामों का यह सेट भारतीय आबादी के एक उपसमुच्चय में परिवेशी वायु प्रदूषण (AP) के कारण होने वाली असामयिक गैर-आकस्मिक कारण-विशिष्ट मृत्यु दर के सापेक्ष जोखिम (RR) अनुमानों का दस्तावेजीकरण करने वाले कारण साक्ष्य के रूप में कार्य कर सकता है।

ABSTRACT. We applied inverse probability weighting (IPW) causal modeling with three air pollutants (PM2.5, O3, and NO2), meteorological parameters, and potential lag effect of exposures to estimate the marginal effect of short-term exposure to air pollution (AP) on cause-specific mortality risks in the Indo-Gangetic Plain (IGP). A causal linkage between short-term exposure to PM2.5 and O3 was found and all the four assessed causes of deaths (viz. neurological, respiratory, cardiovascular, and nephrological deaths), whereas the NO2 was found to have a linkage only with the cardiovascular mortality risks—for every 10-ppb increase in NO2 exposure, the mean risk increased by 0.84% (95% Confidence Interval (CI) = 0.58, 1.10). For every 10 µg m-3 increase in short-term PM2.5 exposure, the increase in the risk of in-hospital all-cause deaths, neurological deaths, respiratory deaths, cardiovascular deaths, and nephrological deaths was 1.76% (1.57, 1.95), 0.28% (0.07, 0.50), 0.73% (0.47, 0.98), 0.72% (0.48, 0.96), and 0.11% (0.09, 0.14), respectively. Likewise, after controlling for PM2.5 and NO2, the causational linkage between acute exposure to O3 and respiratory mortality risk was found to be highest among all studied scenarios—for every 10-ppb increase in O3 there was a 2.24% increase in the respiratory death risk (2.02, 2.45). This set of results from IPW causal modeling could serve as the causational evidence documenting relative risk (RR) estimates of premature non-accidental cause-specific mortalities attributable to ambient AP in a subset of Indian population.

Key words – Air Pollution; Cause-specific mortalities; IPW; Causal inference; India.

1. Introduction

Per recent estimates, the AP is responsible for ~7 million premature deaths globally resulting in an annual economic burden of more than $2.9 trillion (CREA, 2020; WHO, 2014). Furthermore, the ambient air pollution (AAP) has been linked with about 3.7 million premature deaths annually (WHO, 2014). From the public health perspectives, the WHO has revised the air quality (AQ) guidelines recently to achieving clean air for all and for the larger health co-benefits (WHO, 2021). According to the latest report on world air quality, 37 out of 40 top-most polluted cities in the world are situated in South Asia having annually averaged $PM_{2.5}$ concentrations (for year 2020) exceeding over 10 times than the WHO AQ guidelines value (of 5 $\mu g\ m^{-3}$) with highest concentrations observed during the months of October through February (IQAir, 2021). There are a lot of potential evidence and estimates of RR (mortality risk) due to AP from the North American/European regional studies, however, the highly polluted regions in South Asia remain somewhat less studied. Furthermore, RRs reported previously from the Indian region are mostly based on association modeling for AP and all-cause mortality, but the causal modeling estimates are rare assessing the effect of acute exposure to AP on cause-specific mortality risks to our knowledge.

AP represents among the top risk factors for premature deaths in South Asia and is responsible for around 11% of all-cause deaths (non-accidental) and 40 million disability-adjusted life years (IQAir, 2021; de Bont *et al*., 2025; George *et al*., 2025). According to a recent study from India, around 1.24 million deaths annually were shown to be associated with AP, of which 21% (= 0.26 million) and 7.8% (= 0.096 million) have been suggested from the states of Uttar Pradesh (UP) and Bihar (Balakrishnan *et al*., 2019)—both UP and Bihar states are situated in northern part of India within the Indo-Gangetic Plain (IGP). The current study, on the causal effects of air pollution and cause-specific mortality, has been conducted from the holy city of Varanasi (located in eastern part of UP) wherein by-and-large the patients from east UP and west Bihar regions (as revealed in this study and also discussed in the subsequent sections) visit and if required go for admission to the biggest tertiary care public hospital in the region (viz. Sir Sunderlal hospital affiliated with the Institute of Medical Sciences, Banaras Hindu University). Previous research from the study location at Varanasi has documented the acute effects of air pollution and extreme ambient temperatures on all-cause mortality (Singh *et al*., 2021a & b, 2019; Chaudhary *et al*., 2024).

Atmospheric exposures (to O_3, NO_X, and particulate matter: PM) and public health research across the globe in the last 30 years or so documented several insights on the severity of air pollution and distinct health effects, for example (Apte *et al*., 2015; Cohen *et al*., 2005; Dockery *et al*., 1993; Igelström *et al*., 2022; Krishna *et al*., 2021; Lelieveld *et al*., 2015; Limaye *et al*., 2022; Morawska *et al*., 2021; Orellano *et al*., 2020; Qiu *et al*., 2020; USEPA, 2024; Zheng *et al*., 2021). Epidemiological research has revealed that the fine particles when inhaled can increase toxicity even at small mass concentrations because of their large surface area as well as their ability to translocate from the lungs to other organs and tissues, for example (Phalen and Phalen, 2013). Because the chemical composition of PM can vary substantially by season and region, the results from epidemiological studies on PM air pollution are highly variable, and sometimes even contradictory (Phalen and Phalen, 2013). Besides the fine particles, it is also important to assess the health effects of gaseous pollutants (like NO_X, SO_2, and O_3) which can be found in substantial concentrations; each of these pollutants can produce adverse health effects beyond a threshold concentration. That being said, the major objectives of this study were to: (i) estimate the causal effect of exposure to ambient air pollution ($PM_{2.5}$, O_3, and NO_2) on percent increase in cause-specific mortality risks (viz. cardiovascular, respiratory, neurological, and nephrological) in the IGP, and (ii) establish the exposure-response relationships for each of these cause-specific death risks under high ambient concentrations of multiple air pollutants for a subset of Indian population after adjusting for the time-trend, lag effects, and meteorological factors viz. RH, and maximum and minimum temperatures. This study presents an attempt from the Indian region to address the causal linkage between air pollution and cause-specific deaths which is likely to happen via damaging human brain (neurological deaths), lungs (respiratory deaths), heart (cardiovascular deaths), and kidneys (nephrological deaths). We have followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting this observational study (von Elm *et al*., 2007).

2. Data and methodology

2.1. *Study domain*

The spatial area covered in this study, comprising of east Uttar Pradesh (UP) and west Bihar region, was 219,876 sq. km (Fig. 1(a-e)). The average altitude of both the east UP and west Bihar region is typically <100 m above the mean sea level. The study region lies in the IGP which is one of the most populous and among the global hotspots of air pollution (Shaw *et al*., 2024). It is worthwhile mentioning here that a previous study has suggested that emission sources within a city (of IGP) contributes to ~75% of the total $PM_{2.5}$ whereas the

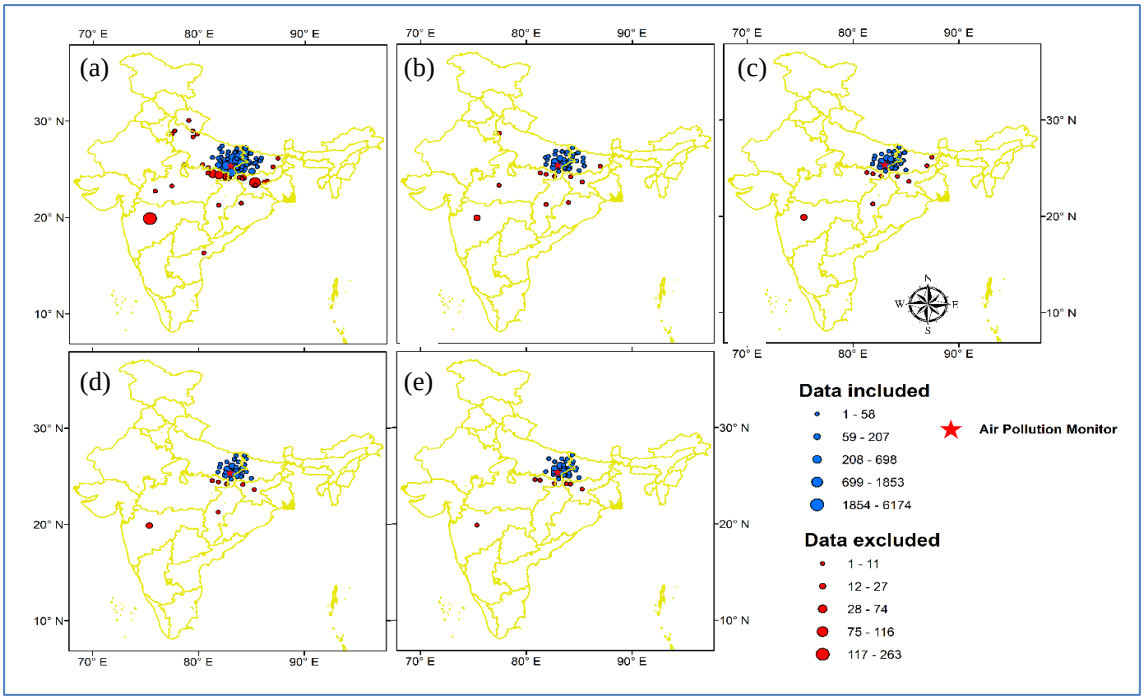

Fig. 1(a-e). Map of India with graduated symbols for: (a) In-hospital all-cause deaths, (b) Neurological deaths, (c) Respiratory deaths, (d) Cardiovascular deaths, and (e) Nephrological deaths during the entire study period. Graduated symbols indicate the density of patients admitted from Varanasi or neighboring cities to the SSlal hospital (BHU, Varanasi)

remaining 25% is being contributed by the long-range transport of air-masses from the upwind region (Rajput *et al*., 2021). The study region experiences typical tropical climatic conditions with hot and moist summers and cold winters. The total population of actual study area (covering east UP and west Bihar) per the latest census of 2011 was 109,702,736 of which females were 53,166,628 and males were 56,536,108 (Table S1) (Census, 2011).

2.2. *Exposure and Covariates data*

We have retrieved the daily averaged open-source data of $PM_{2.5}$, O_3, NO_2, SO_2, and PM_{10} for Varanasi city center (monitoring location: Ardali Bazar) for the period 01st Jan 2012 to 31st Dec 2018 from the India's Central Pollution Control Board (CPCB, 2021). The uncertainty in the measurements of $PM_{2.5}$ was <5% (given in the links: https://cpcb.nic.in/openpdffile.php?id=TGF0ZXN0RmlsZS8zNjRfMTY3NTk0NTY0Ml9tZWRpYXBob3RvMjU2NDQucGRm;https://cpcb.nic.in/openpdffile.php?id=UmVwb3J0RmlsZXMvMjdfMTQ1ODExMDQyNl9OZXdJdGVtXzE5Nl9OQUFRTVNfVm9sdW1lLUkucGRm). For other air pollutants, we could not Figure out the measurement uncertainty from the CPCB website. The calibration and quality checks of all monitors were done routinely as per the CPCB. Though all details are not given on any open platform for further use but some information about calibration can be found at (https://cpcb.nic.in/openpdffile.php?id=UmVwb3J0RmlsZXMvMjdfMTQ1ODExMDQyNl9OZXdJdGVtXzE5Nl9OQUFRTVNfVm9sdW1lLUkucGRm;https://cpcb.nic.in/openpdffile.php?id=UmVwb3J0RmlsZXMvOTM4XzE1NjQ2NTIzNzdfbWVkaWFwaG90bzc3MjEucGRm). Some details on methodology and calibration frequency are also given in public domain at (https://cpcb.nic.in/displaypdf.php?id=c291cmNlYXBwb3J0aW9ubWVudHN0dWRpZXMucGRm;https://cpcb.nic.in/openpdffile.php?id=UmVwb3J0RmlsZXMvMjMyXzE0OTU3MTE5NjJfbWVkaWFwaG90bzEyMjA3LnBkZg==).

To strengthen the modeling exercise and enhance robustness of the interpretation, the outliers in the data set of air pollutants, falling outside 2.5th–97.5th percentiles, were not considered in this study. We noticed that retrieved $PM_{2.5}$ data were missing for several days (= 42%) during the study period between 2012 and 2018 and were therefore imputed using the random forest machine learning algorithm (reference is made to supplemental information). The missing value imputation was done only for $PM_{2.5}$ using PM_{10}, RH, temperatures, SO_2, NO_2, and O_3 (Fig 2 and Fig. S1, Fig. S2) because it's not only about applying the machine learning algorithm to impute missing $PM_{2.5}$ but also the imputation model was built from the subject matter knowledge-like $PM_{2.5}$ is contained in PM_{10}, and a substantial mass fraction of $PM_{2.5}$ can form from atmospheric chemical reactions of SO_2, NO_2, and O_3 under varying RH and temperature conditions both during the day and in the night. On the other hand, such evidence

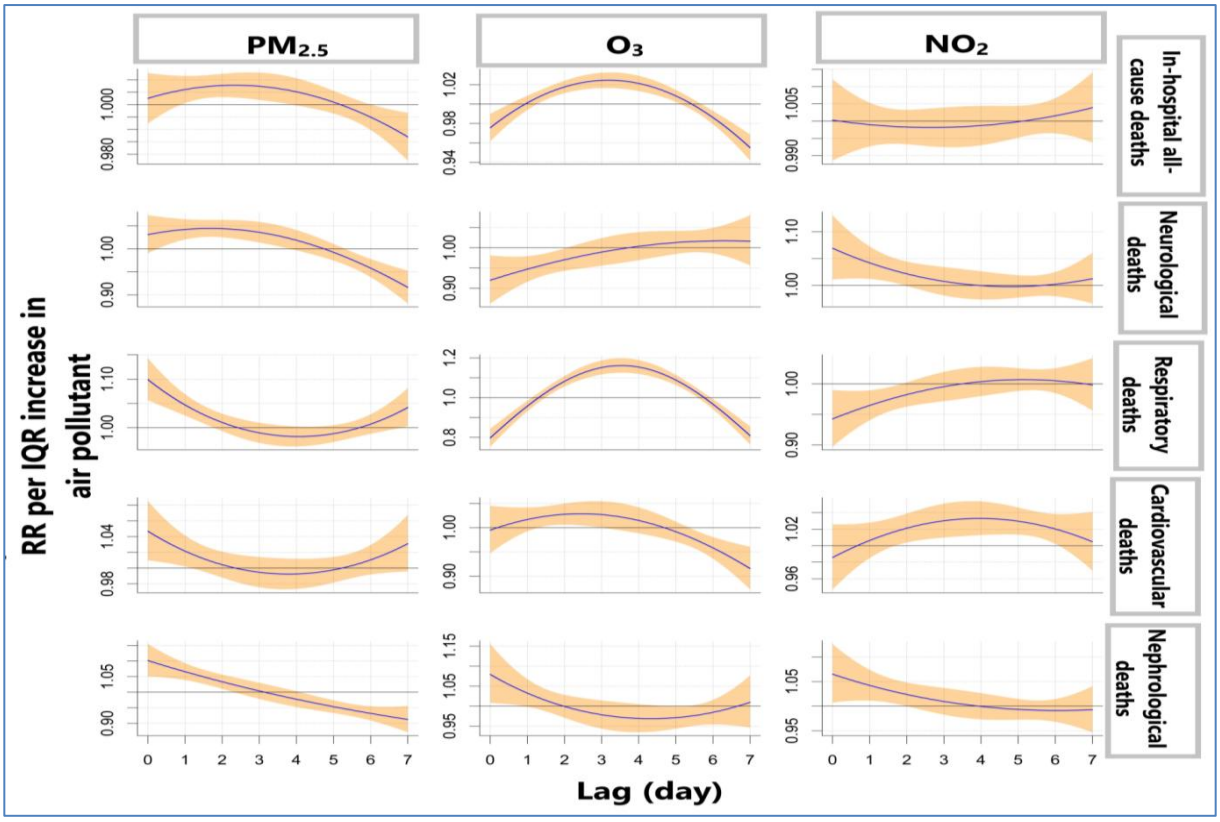

Fig. 2. Mortality risks (and 95% CI) per IQR increase in air pollutants ($PM_{2.5}$, O_3, and NO_2) at different lags from the distributed lag model for in-hospital all-cause deaths; neurological deaths; respiratory deaths; cardiovascular deaths; and nephrological deaths

was not available to us for the gaseous pollutants and so we did not impute gaseous pollutants from $PM_{2.5}$, PM_{10} or other set of gaseous pollutants considered in this study. Ambient meteorological data set for the entire period over Varanasi city including maximum and minimum temperatures (T_{max}, T_{min}; in °C), and relative humidity (RH, in %), have been retrieved from the India Meteorological Department. The measurements of meteorological parameters by IMD are highly accurate: uncertainty of 0.1 K for temperature and 1% for RH (https://camd.imd.gov.in/wmo/pdf/WMO-No-8 Guide%20 to%20Meteorological%20Instruments%20and%20Method %20of%20Observations-2010.pdf). The IMD monitoring station in Varanasi is in Babatpur (25.448313 °N, 82.852043 °E). The correlation between air pollutants and variability in their mass concentrations are given in supplemental information (Fig. S3, Fig. S4). The monthly variability in meteorological parameters (RH, T_{max}, and T_{min}) used in this study is also given in supplemental information (Fig. S5).

2.3. *Outcome data*

The health records of daily cause-specific mortalities were collected for the study period from 1st Jan 2012–31st Dec 2018 from Sir Sunderlal (SSlal) Hospital, located within the premises of Banaras Hindu University campus (BHU, in Varanasi, Uttar Pradesh). The SSlal hospital is the largest tertiary care hospital in the region wherein many patients visit daily from the city and nearby districts and states. The daily mortality records were categorized as per the International Classification of Diseases 10th revision according to the sex and age group into: (i) all neurological deaths (ICD-10: G00–G99), (ii) respiratory deaths (ICD-10: J00–J98), (iii) cardiovascular deaths (ICD-10: I00–I99), (iv) nephrological deaths (ICD-10: N00–N99), and (v) other deaths (ICD-10: A00–B99, C00–D48, D50–D89, E00–E89, F00–F99, H00–H59, H60–H95, K00–E93, L00–L98, O00–O99, S00–T98, V01–Y98). All these cause-specific deaths (sum of i to v) were pooled together and represented as "in-hospital all-cause deaths" (Table 1). The non-institutional deaths were not included in this study simply because we wanted to avoid any human error occurring in maintaining the health register of births and deaths (Nori-Sarma *et al*., 2017). A team of public health researchers from India have recently mentioned an urgent need for a good quality segregation of causes of mortality records in the register of births and deaths (Dutta *et al*., 2022). For the cause-specific deaths, in this study, we solely relied therefore on the hospital records.

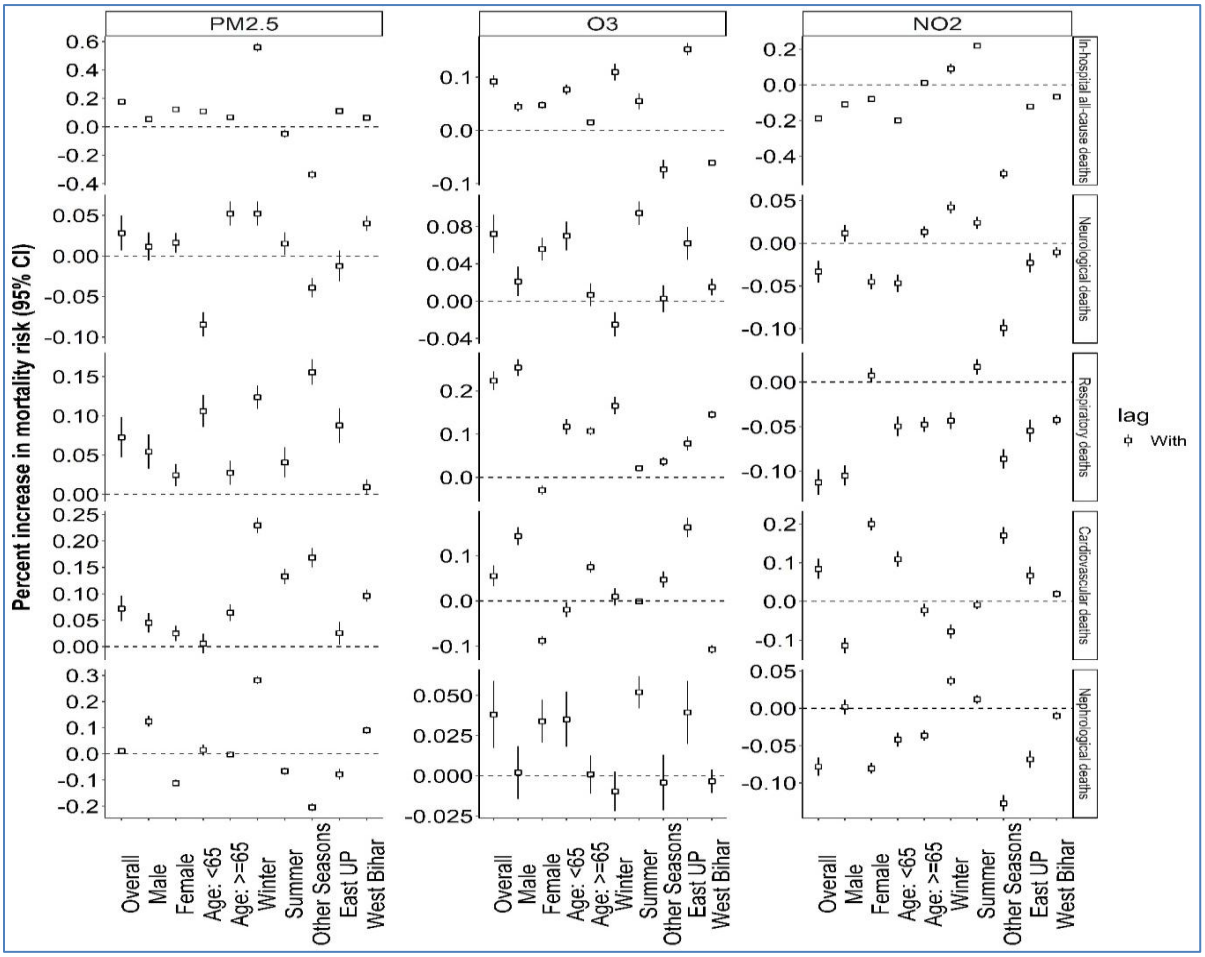

Fig. 3. Marginal estimates of percent increase (and 95% CI) in daily adjusted mortality risks associated with a 1 unit increase in $PM_{2.5}$, O_3, and NO_2 by sex, age, season, and region (accounting for the lag effect)

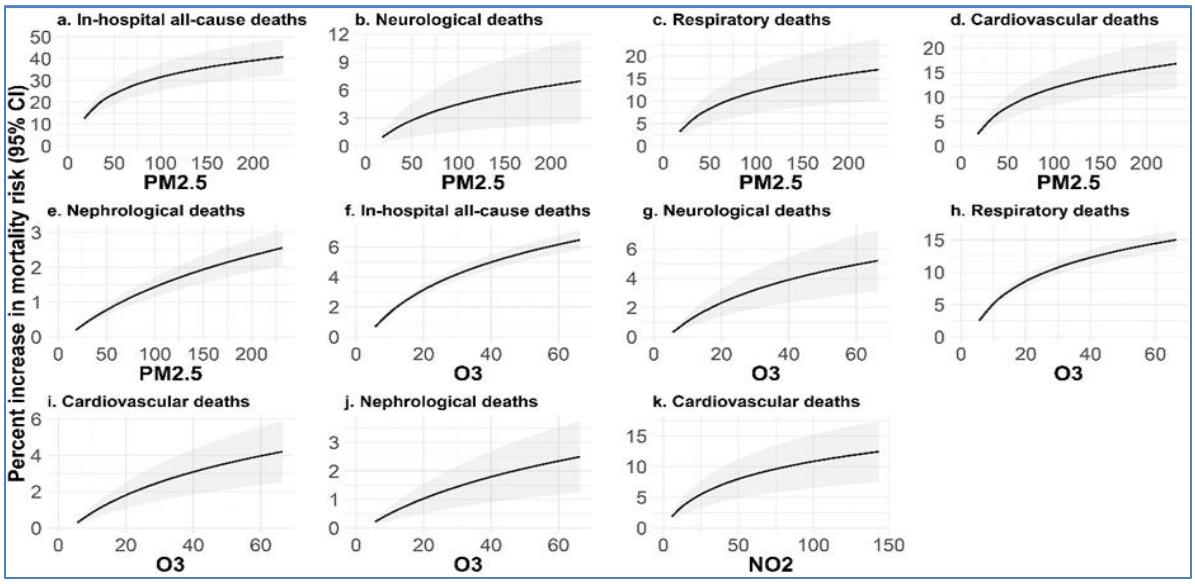

Fig. 4. Exposure-response relationships, based on IPW causal modeling, between $PM_{2.5}$, O_3, and NO_2 exposures and cause-specific mortality (viz. in-hospital all-cause deaths, neurological deaths, respiratory deaths, cardiovascular deaths, and nephrological deaths) risks for the period 2012– 2018

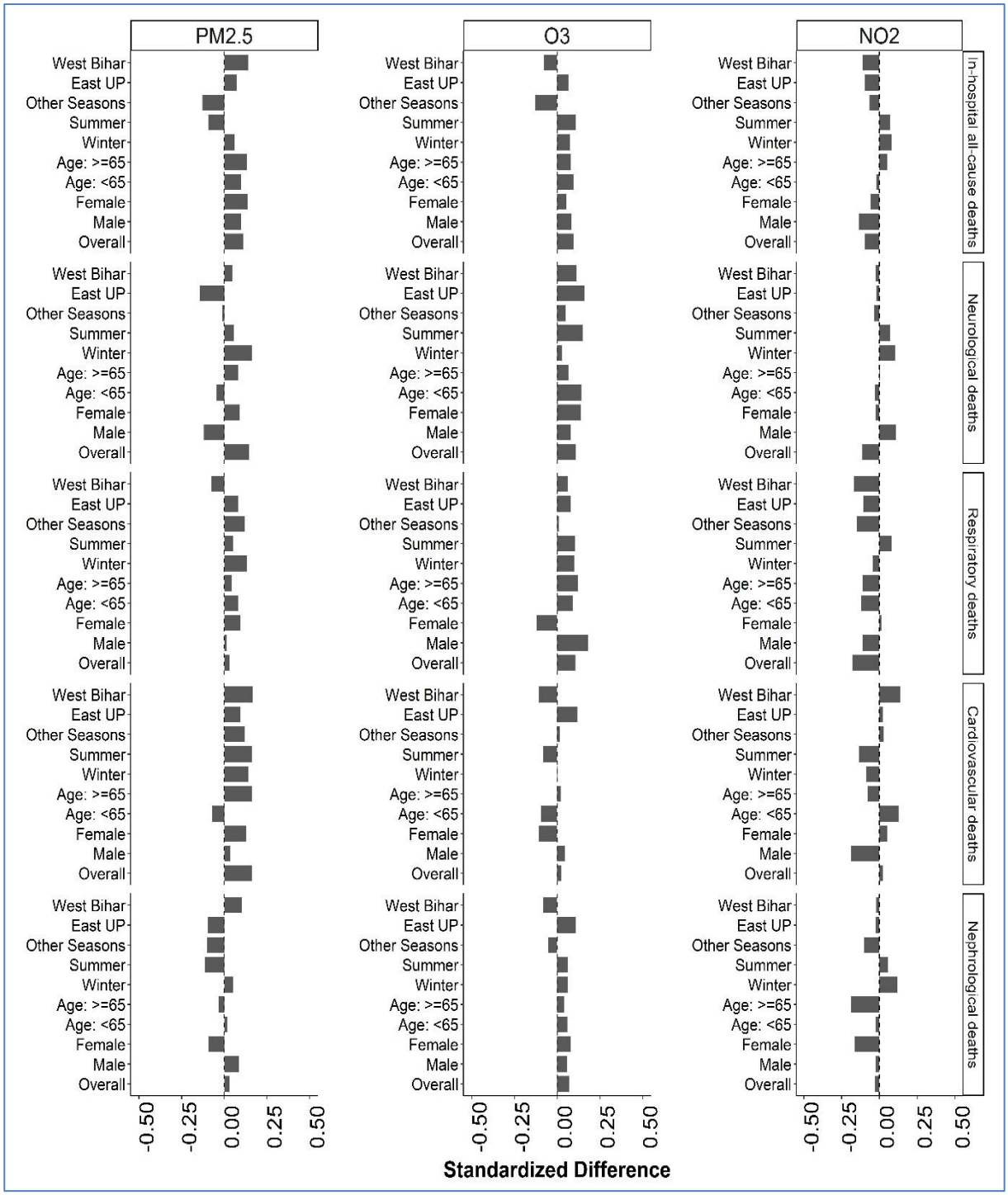

Fig. 5. Standardized mean differences in covariates between observations above and below the mean exposure ($PM_{2.5}$, O_3, and NO_2) concentrations (for mean concentrations reference is made to table 2) after applying inverse probability weighting (IPW) using the generalized propensity scores

TABLE 1

Characteristics of in-hospital all-cause mortality and cause-specific mortalities in the central Indo-Gangetic Plain (IGP), 2012–2018

Category	Total deaths (% of total)	Mean daily deaths (SD)
In-hospital all-cause deaths	22890 (100)	8.9 (3.4)
Sex		
Female	9795 (42.8)	3.8 (2.1)
Male	13095 (57.2)	5.1 (2.4)
Age group		
< 65 Y	17175 (75.0)	6.7 (2.9)
≥ 65 Y	5715 (25.0)	2.2 (1.5)
Season		
Winter	5873 (25.7)	2.3 (4.4)
Summer	5848 (25.5)	2.3(4.3)
Other Seasons	11169 (48.8)	4.4(4.9)
Region		
East UP	18162 (79.3)	7.1 (3.3)
West Bihar	4728 (20.7)	1.8 (1.6)
Neurological deaths	1613 (100)	0.6 (0.9)
Sex		
Female	588 (36.5)	0.2 (0.5)
Male	1025 (63.5)	0.4 (0.7)
Age group		
< 65 Y	1024 (63.5)	0.4 (0.7)
≥ 65 Y	589 (36.5)	0.2 (0.5)
Season		
Winter	469 (29.1)	0.2 (0.6)
Summer	497 (30.8)	0.2 (0.6)
Other Seasons	647 (40.1)	0.3 (0.6)
Region		
East UP	1282 (79.5)	0.5 (0.8)
West Bihar	331 (20.5)	0.1 (0.4)
Respiratory deaths	1497 (100)	0.6 (0.8)
Sex		
Female	586 (39.1)	0.2 (0.5)
Male	911 (60.9)	0.4 (0.6)
Age group		
< 65 Y	989 (66.1)	0.4 (0.6)
≥ 65 Y	508 (33.9)	0.2 (0.4)
Season		
Winter	354 (23.6)	0.1 (0.5)
Summer	437 (29.2)	0.2 (0.5)
Other Seasons	7106 (47.2)	0.3 (0.6)
Region		
East UP	1263 (84.4)	0.5 (0.7)
West Bihar	234 (15.6)	0.1 (0.3)
Cardiovascular deaths	1499 (100)	0.6 (0.8)
Sex		
Female	587 (39.2)	0.2 (0.5)
Male	912 (60.8)	0.4 (0.6)
Age group		
< 65 Y	832 (55.5)	0.3 (0.6)
≥ 65 Y	667 (44.5)	0.3 (0.5)

Table 1 Continued

Category	Total deaths (% of total)	Mean daily deaths (SD)
	Season	
Winter	401 (26.8)	0.2 (0.5)
Summer	348 (23.2)	0.1 (0.4)
Other Seasons	750 (50.0)	0.3 (0.6)
	Region	
East UP	1270 (84.7)	0.5 (0.7)
West Bihar	229 (15.3)	0.1 (0.3)
Nephrological deaths	1100 (100)	0.4 (0.7)
	Sex	
Female	415 (37.7)	0.2 (0.4)
Male	685 (62.3)	0.3 (0.5)
Age group		
< 65 Y	773 (70.3)	0.3 (0.6)
≥ 65 Y	327 (29.7)	0.1 (0.4)
	Season	
Winter	289 (26.3)	0.1 (0.4)
Summer	237 (21.5)	0.1 (0.4)
Other Seasons	574 (52.2)	0.2 (0.5)
	Region	
East UP	920 (83.6)	0.4 (0.6)
West Bihar	180 (16.4)	0.1 (0.3)

Furthermore, we could get access to the health records of cause-specific mortality data from SSlal Hospital from 2012 to 2018 only. The effect of COVID-19 pandemic was severely noticed in 2020 and 2021 in India and across the globe during which substantial number of associated mortalities were observed. Since then, we could not get access to the cause-specific mortality record from the hospital.

2.4. *Association modeling approach*

First, we assessed the association between AP ($PM_{2.5}$, O_3, and NO_2) and health outcomes (cause-specific mortalities: neurological deaths, respiratory deaths, cardiovascular deaths, nephrological deaths, and in-hospital all-cause deaths). The generalized additive quasi-Poisson time-series regression models for each of the cause-specific deaths and in-hospital all-cause deaths were built as given below:

$$\begin{aligned} Log(\mathrm{E}[Mortality_t]) &= \beta_0 + \beta_1 . PM_{2.5_t} + \beta_2 . O_{3_t} \\ &+ \beta_3 . NO_{2_t} + s(Tmax_t) \\ &+ s(Tmin_t) + s(RH_t) \\ &+ \beta_4 . DOW_t + s(Time_t, df \\ &= 5/year) \end{aligned}$$

here, β_0 represents intercept of the model, β_1–β_4 are the regression coefficients, $PM_{2.5}$, O_3, and NO_2 are multi-air pollutants measured at a time t, s represents the penalized cubic spline function operated on Tmax, Tmin, and RH whereas for "Time" variable the spline with a 5 degrees of freedom (df) per year was applied (Kloog *et al*., 2013; Wood, 2006). Also, the model accounted for day-of-the week (DOW). The above-mentioned model is termed as the "Basic" model. Subsequently, we determined the lag-effect of AP exposure variables and for the RH (lag 1) and incorporated in the "Basic" model and termed it as the "First-Gen" model. The description of "First-Gen" model is given in the subsequent section; the "Basic" model was only used until the estimation of lag-effects. All results obtained from "First-Gen" model are given in supplemental information. We have also carried out a separate set of analysis assessing the association between AP and cause-specific deaths for the Varanasi city only, using the same time-series model as discussed above ("Basic" and "First-Gen" models). All results, including those for Varanasi health records only, are given in supplemental information (Tables S2, S3, S4 and Fig. S7, Fig S8).

2.5. *Sensitivity analysis of lag effects*

We have performed sensitivity analyses of lag effects to evaluate the robustness of the results. The lag effect up to 7-days of a single exposure variable ($PM_{2.5}$, O_3, or NO_2; one at a time) on cause-specific mortalities

TABLE 2

Summary statistics of air pollution ($PM_{2.5}$, O_3, and NO_2), and weather (maximum and minimum temperatures, and relative humidity) data in Varanasi for the entire study period of 2012–2018

Air Pollutant conc. (24-h average)	No. of observations (N)	Mean ± SD	Min.	P(25)	Median	P(75)	Max.	IQR
$PM_{2.5}$ (μg m^{-3})	1616	84.7 ± 46.2	17.7	47.6	83.7	106.9	231.9	59.3
Season								
Winter	688	114.6 ± 41.7	19.0	90.5	104.7	132.2	231.9	41.7
Summer	601	77.0 ± 35.7	17.7	51.4	72.5	96	225.4	44.6
Other Seasons	327	36.2 ± 14.7	17.7	24.7	33.2	42.9	95.6	18.2
O_3 (ppb)	1616	20.6 ± 13.2	5.6	11.2	16.3	25.9	66.4	14.7
Season								
Winter	688	17.5 ± 10.4	5.6	11.2	15.4	20.1	66.4	8.9
Summer	601	25.8 ± 13.6	5.7	13.8	23.9	34.1	66.3	20.3
Other Seasons	327	17.6 ± 14.6	5.6	8.4	11.5	18.1	65.1	9.7
NO_2 (ppb)	1616	31.9± 27.7	5.7	16.6	23.6	32.6	143.2	16.0
Season								
Winter	688	41.4 ± 33.4	5.7	22.3	29.1	37.8	143.2	15.5
Summer	601	29.2 ± 22.9	6.4	16.3	22.3	31.2	143.0	14.9
Other Seasons	327	17.2 ± 8.6	5.9	12.2	15.0	20.2	73.6	8.0
Meteorological data (24-h average)								
Max. Temp (°C)	1616	31.7 ± 6.8	10.6	27.0	32.4	36.5	46.0	9.5
Season								
Winter	688	26.2 ± 5.2	10.6	22.6	26.6	30.4	36.9	7.8
Summer	601	37.3 ± 4.7	20.8	34.4	38.4	41.0	46.0	6.6
Other Seasons	327	32.9 ± 2.4	25.4	32.0	33.3	34.3	39.7	2.3
Min. Temp (°C)	1616	20.3 ± 7.1	4.2	14.2	21.7	26.5	33.3	12.3
Season								
Winter	688	14.2 ± 5.2	4.2	10.3	13.4	17.6	28.0	7.3
Summer	601	24.0 ± 5.0	10.2	20.8	25.0	28.0	33.3	7.2
Other Seasons	327	26.5 ± 1.5	22.2	25.5	26.6	27.6	32.4	2.1
RH (%)	1616	63.6 ± 17.0	17.5	52.0	66.0	77.0	98.5	25.0
Season								
Winter	688	70.2 ± 10.2	32.5	63.0	70.0	77.0	98.0	14.0
Summer	601	47.8 ± 13.9	17.5	37.0	48.0	56.5	98.0	19.5
Other Seasons	327	78.9 ± 9.2	39.5	73.5	79.5	84.8	98.5	11.3

P(25) and P(75) are the 25th and 75th percentile. IQR is interquartile range. The period from October to February is usually high air pollution period and is represented herein as winter, from March to May as summer, and from June to September as Other Seasons.

has been assessed using the distributed lag nonlinear model (Gasparrini, 2011). Specifically, the mortality risks per IQR (interquartile range) increase in concentrations of air pollutants ($PM_{2.5}$, O_3, and NO_2) at different lags (0–7 days) were estimated using the distributed lag model for: in-hospital all-cause deaths, neurological deaths, respiratory deaths, cardiovascular deaths, and nephrological deaths. Briefly, for the cause-specific mortalities, a separate 2-D matrix was generated that contained exposure metric representing the moving average term for each of the exposure variables ($PM_{2.5}$, O_3, or NO_2) with a lag (0–x, where x = up to previous 7-days). The mortality risks (RR) per interquartile range (IQR) increase in predictors ($PM_{2.5}$, O_3, and NO_2) at different lags (0–7 days) were estimated using the distributed lag model (Table 2).

TABLE 3

Marginal estimates, based on inverse probability weighting (IPW) causal modeling, of percent increase in adjusted mortality risk (and 95% CI) for specific causes of death for a 10 μg m^{-3} change in $PM_{2.5}$, O_3, or NO_2 exposure

Cause of Death	$PM_{2.5}$		O_3		NO_2	
	% change in mortality		% change in mortality		% change in mortality	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
In-hospital all-cause deaths						
Overall	**1.76**	**(1.57, 1.95)**	**0.92**	**(0.81, 1.03)**	-1.88	(-2.06, -1.71)
Male	**0.53**	**(0.38, 0.67)**	**0.45**	**(0.36, 0.53)**	-1.10	(-1.23, -0.96)
Female	**1.23**	**(1.10, 1.36)**	**0.47**	**(0.40, 0.55)**	-0.79	(-0.89, -0.68)
Age: <65	**1.09**	**(0.93, 1.25)**	**0.77**	**(0.67, 0.86)**	-1.99	(-2.14, -1.85)
Age: >=65	**0.67**	**(0.58, 0.75)**	**0.15**	**(0.10, 0.21)**	**0.11**	**(0.03, 0.20)**
Winter	**5.59**	**(5.29, 5.89)**	**1.10**	**(0.94, 1.26)**	**0.90**	**(0.62, 1.18)**
Summer	-0.48	(-0.74, -0.22)	**0.55**	**(0.40, 0.70)**	**2.20**	**(2.05, 2.34)**
Other Seasons	-3.36	(-3.64, -3.07)	-0.73	(-0.90, -0.55)	-4.99	(-5.25, -4.72)
East UP	**1.12**	**(0.92, 1.31)**	**1.53**	**(1.41, 1.64)**	-1.22	(-1.38, -1.06)
West Bihar	**0.64**	**(0.53, 0.75)**	-0.61	(-0.66, -0.55)	-0.66	(-0.74, -0.59)
Neurological deaths						
Overall	**0.28**	**(0.07, 0.50)**	**0.72**	**(0.51, 0.93)**	-0.33	(-0.46, -0.21)
Male	0.12	(-0.06, 0.29)	**0.21**	**(0.05, 0.37)**	**0.12**	**(0.02, 0.21)**
Female	**0.16**	**(0.04, 0.28)**	**0.56**	**(0.44, 0.68)**	-0.45	(-0.54, -0.36)
Age: <65	-0.84	(-1.00, -0.69)	**0.70**	**(0.55, 0.86)**	-0.47	(-0.57, -0.36)
Age: >=65	**0.52**	**(0.37, 0.67)**	0.07	(-0.05, 0.19)	**0.13**	**(0.07, 0.20)**
Winter	**0.52**	**(0.37, 0.67)**	-0.25	(-0.38, -0.12)	**0.42**	**(0.35, 0.49)**
Summer	**0.15**	**(0.01, 0.29)**	**0.94**	**(0.82, 1.07)**	**0.24**	**(0.17, 0.31)**
Other Seasons	-0.39	(-0.51, -0.27)	0.03	(-0.12, 0.17)	-0.99	(-1.09, -0.89)
East UP	-0.12	(-0.31, 0.07)	**0.62**	**(0.44, 0.80)**	-0.23	(-0.34, -0.12)
West Bihar	**0.40**	**(0.31, 0.50)**	**0.15**	**(0.06, 0.24)**	-0.11	(-0.17, -0.04)
Respiratory deaths						
Overall	**0.73**	**(0.47, 0.98)**	**2.24**	**(2.02, 2.45)**	-1.12	(-1.27, -0.98)
Male	**0.54**	**(0.32, 0.76)**	**2.54**	**(2.35, 2.73)**	-1.05	(-1.16, -0.93)
Female	**0.24**	**(0.10, 0.39)**	-0.30	(-0.41, -0.19)	0.08	(-0.01, 0.16)
Age: <65	**1.06**	**(0.86, 1.26)**	**1.17**	**(0.99, 1.35)**	-0.50	(-0.61, -0.39)
Age: >=65	**0.28**	**(0.13, 0.43)**	**1.07**	**(0.98, 1.16)**	-0.48	(-0.56, -0.39)
Winter	**1.24**	**(1.09, 1.38)**	**1.66**	**(1.46, 1.86)**	-0.43	(-0.53, -0.34)
Summer	**0.41**	**(0.22, 0.60)**	**0.22**	**(0.17, 0.26)**	**0.17**	**(0.09, 0.25)**
Other Seasons	**1.56**	**(1.39, 1.72)**	**0.36**	**(0.26, 0.46)**	-0.86	(-0.97, -0.75)
East UP	**0.88**	**(0.66, 1.10)**	**0.78**	**(0.62, 0.94)**	-0.55	(-0.67, -0.42)
West Bihar	0.09	(-0.01, 0.19)	**1.46**	**(1.37, 1.54)**	-0.43	(-0.48, -0.37)
Cardiovascular deaths						
Overall	**0.72**	**(0.48, 0.96)**	**0.55**	**(0.32, 0.78)**	**0.84**	**(0.58, 1.10)**
Male	**0.45**	**(0.26, 0.64)**	**1.43**	**(1.24, 1.62)**	-1.14	(-1.34, -0.94)
Female	**0.25**	**(0.11, 0.40)**	-0.88	(-0.99, -0.77)	**2.00**	**(1.84, 2.16)**
Age: <65	0.06	(-0.12, 0.25)	-0.19	(-0.36, -0.03)	**1.09**	**(0.89, 1.29)**
Age: >=65	**0.64**	**(0.48, 0.81)**	**0.74**	**(0.62, 0.87)**	-0.23	(-0.39, -0.06)
Winter	**2.29**	**(2.15, 2.44)**	0.09	(-0.10, 0.28)	-0.78	(-0.95, -0.60)
Summer	**1.33**	**(1.18, 1.48)**	-0.01	(-0.05, 0.02)	-0.09	(-0.20, 0.03)
Other Seasons	**1.68**	**(1.50, 1.87)**	**0.47**	**(0.30, 0.65)**	**1.71**	**(1.49, 1.93)**
East UP	**0.26**	**(0.04, 0.47)**	**1.62**	**(1.41, 1.84)**	**0.67**	**(0.44, 0.90)**
West Bihar	**0.96**	**(0.85, 1.08)**	-1.07	(-1.16, -0.98)	**0.19**	**(0.10, 0.29)**

Table 3 continued

Nephrological deaths						
Overall	**0.11**	**(0.09, 0.14)**	**0.38**	**(0.17, 0.59)**	-0.78	(-0.91, -0.66)
Male	**1.25**	**(1.04, 1.45)**	0.02	(-0.14, 0.18)	0.02	(-0.08, 0.12)
Female	-1.12	(-1.25, -0.99)	**0.34**	**(0.21, 0.48)**	-0.80	(-0.88, -0.73)
Age: <65	0.15	(-0.06, 0.36)	**0.35**	**(0.18, 0.52)**	-0.42	(-0.51, -0.32)
Age: >=65	-0.03	(-0.15, 0.09)	0.01	(-0.11, 0.13)	-0.36	(-0.43, -0.29)
Winter	**2.82**	**(2.66, 2.98)**	-0.10	(-0.22, 0.03)	**0.37**	**(0.31, 0.44)**
Summer	-0.66	(-0.81, -0.51)	**0.52**	**(0.42, 0.62)**	**0.12**	**(0.06, 0.18)**
Other Seasons	-2.05	(-2.20, -1.89)	-0.04	(-0.21, 0.13)	-1.27	(-1.38, -1.16)
East UP	-0.78	(-0.99, -0.57)	**0.40**	**(0.20, 0.59)**	-0.68	(-0.80, -0.57)
West Bihar	**0.90**	**(0.77, 1.04)**	-0.03	(-0.11, 0.04)	-0.10	(-0.15, -0.05)

Values in bold are statistically significant ($p < 0.05$)

2.6. *Causal modeling approach*

We fit marginal structural models using weights based on the generalized propensity score (GPS) model (referred to as generalized inverse probability weighting method: IPW) following the methodology proposed by a previous study (Cole and Hernán, 2008). Under the four presumptions of consistency, exchangeability, positivity, and proper specification of the model used to estimate the weights, the IPW method can be used to account for measurable confounding and selection bias (Cole and Hernán, 2008). A generalized IPW method has been used in previous studies, for example (Qiu *et al*., 2020). For each of the exposures we have assessed the distributed lag effect from day 0–5 (lag0 represents the current day of the event whereas lag5 represents 5 days prior to the event (for example, cause-specific deaths in this case). And for each lag of each exposure, a linear regression was fitted with the exposure lag of interest (n^{th}) against all the other (n^{th} -1, refer to Table S5) lags of that pollutant and the six-lags of the other pollutant along with linear and quadratic terms for temperature (lag 0 and 1), and linear terms for relative humidity (lag 0 and 1) to block the backdoor pathway from the previous lag (Di *et al*., 2017). The probability density of the model's residuals represents the likelihood that everyone would experience the exposure predicted by the variables used in generalized propensity score models. These probabilities are further stabilized by dividing with the marginal probability of the exposure the subject received, and the inverse of these probabilities represents corresponding weights for each subject for that lag. We transformed exposures into our model, since most of the observations had high exposure level and approximation to normal distribution could thus be achieved to satisfy the assumption for linear models. Under the assumptions of no important omitted confounders, regressing outcome against exposure at a lag, using the weights specific to that lag, should provide the marginal effect of that lag of that exposure (e.g. PM2.5 lag3), independent of the covariates. This was done for each of the six-lags of each pollutant. We have truncated the weights and s*et al* l weights above the 99^{th} percentile equal to the 99^{th} percentile and all weights below the 1^{st} percentile equal to the 1^{st} percentile to remove the effect of any outliers in the IPW analysis (Cole and Hernán, 2008).

Generalized Propensity Score (GPS) is the probability density function for the residuals of the regression of exposure on confounders. We computed weights and stabilized them by multiplying them with the marginal probability of exposure which is the probability of getting the exposure got in a model with just an intercept; this process seeks to achieve exposure independent of confounders. We use linear regression for the exposure variables (herein, $PM_{2.5}$, O_3, and NO_2)—the probability density of the residuals from this model is the GPS. The GPS is the probability density function of being exposed given the covariates. Weighting by the inverse of the probability density of exposure given covariates is the inverse of the GPS. So, applying appropriate weights to the high vs. low exposure sub-groups makes, in the weighted sample, the exposure uncorrelated with covariates. We reiterate that the application of IPW given the covariates seeks to achieve exposure independent of the potential confounders. Thus, weighting creates a pseudo-population with no association between exposure and potential confounders.

For determining the E-R relationship curve, we have made the use of estimated RR at each of the daily averaged exposure values from the IPW causal modeling. The relation between RR and percent increase in mortality risk can be given by the formula [percent increase in mortality risk = (RR-1) x 100]. A GAM model was used to fit log-linear relationship between daily averaged exposure values of $PM_{2.5}/O_3/NO_2$ and the percent increase in mortality risks (and 95% CI) (for the significant overall

scenarios, please refer to Table 3). We subsequently computed the standardized differences for covariates by dividing the mean differences by their standard deviations. We ran weighted linear regressions with exposure as the only variable and got unconfounded (by measured covariates) estimates of β (Hernán and Robins, 2020), and of the marginal probability of dying as a function of exposure. We included all the necessary terms, as aforementioned, in the GPS model and achieved balanced covariates above and below mean exposure variables ($PM_{2.5}$, O_3, or NO_2). The sensitivity analysis for robustness to unmeasured confounding has also been carried out in this study using the E-value which is a measurement of how strong an unobserved confounder should be to explain away the observed associations (VanderWeele and Ding, 2017). To address the measurement uncertainty and spatial variability, we have done an additional sensitivity analysis wherein we imposed ±30% shift in the distribution of each of the air pollutants ($PM_{2.5}$, O_3, and NO_X). The information on overall spatial variability of air pollution over the study region (east UP-west Bihar) has been inferred from a recent study on long-term exposure to air pollution and health effects (Brown *et al*., 2022).

2.7. *Effect modification/Subgroup analysis*

Effect modification is a stratum-specific measure of association/causation (RR) that changes as a function of subgroup analysis. Effect modification analysis is very important in epidemiological studies because it allows us to infer about high- versus low-risk subgroups. In this study, each cause-specific mortality risk analysis was stratified by sex (M, F), age (<65, ≥ 65), season (considered heavy air pollution episode & winter as winter: Oct–Feb; summer: Mar–May; other seasons: June–Sept), and region (east UP, west Bihar).

3. Results and discussion

The spatial domain covered in this study comprised of east Uttar Pradesh (UP) and west Bihar region (Fig. 1). The demographic statistics of cause-specific deaths registered at the SSlal-hospital for the patients visiting from east UP and west Bihar regions for years 2012–2018 are summarized in Table 1. The total (or pooled) non-accidental in-hospital deaths (referred hereafter as the "in-hospital all-cause deaths") were 22,890, with an average of 8.9 deaths/day. Furthermore, there were 1613 deaths due to neurological disorders, 1497 deaths due to respiratory disorders, 1499 due to cardiovascular disorders, and 1100 deaths due to nephrological disorders. The mean daily deaths for these four cause-specific mortalities ranged from 0.4–0.6. The period from October to February, integrated herein as winter, is basically a period marked with very poor air quality over entire IGP region (Jethva *et al*., 2019). For all these specific details on cause-specific mortality records the reference is made to Table 1. Table 2 presents the descriptive statistics of daily $PM_{2.5}$, O_3, NO_2, maximum and minimum temperatures, and relative humidity for Varanasi for the entire study period of 2012–2018. In the current study, from IGP region, the daily averaged ambient concentrations of $PM_{2.5}$, O_3, and NO_2 varied from 17.7–231.9 μg m^{-3}, 5.6–143.2 ppb, and 5.7–143.2 ppb, respectively.

The results of mortality risks per IQR (interquartile range) increase in concentrations of air pollutants ($PM_{2.5}$, O_3, and NO_2) at distributed lags (0–7 days) for in-hospital all-cause deaths, neurological deaths, respiratory deaths, cardiovascular deaths, and nephrological deaths have been estimated (and shown in Fig. 2). The sensitivity analysis was carried out for accounting the lag between exposure and the event of death, in the quasi-Poisson time-series model. The distributed lag period (in days) estimations of air pollutants for the in-hospital all-cause mortality risk and cause-specific mortality risks have been summarized in Table S5 (also shown in Fig. 2). Accordingly, either there was a lag effect between an exposure variable and an outcome or there was no lag-effect (represented by NA in Table S5) (Fig. 2, Table S5). Accounting for the lag effect is very important while determining the association of air pollution (AP) and health risk. The final exposure metric up to the distributed lag was considered where the RR is statistically significant (i.e., the cumulative lag effect) and was incorporated in the quasi-Poisson time-series model separately for each of the pollutants. The cases wherein the lag effect (in days) of an exposure variable was observed, we have taken that into account in the IPW causal modeling. Effect modifications due to sex (M, F), age (<65, ≥ 65), season (winter: Oct–Feb; summer: Mar–May; other seasons: June–Sept), and region (east UP, west Bihar) have also been examined in this study.

Fig. 3 shows the marginal estimates of percent increase in adjusted mortality risks associated with a 1 unit increase in $PM_{2.5}$ or O_3 or NO_2 by sex, age, season, and region for the cumulative lag effect. Overall, after adjusting for $PM_{2.5}$ and O_3, the effect of NO_2 on cause-specific mortality risks was found to be significant only for cardiovascular mortality risk [for every 10-ppb increase in NO_2 exposure the risk increased by 0.84% (95% CI = 0.58, 1.10)] (Table 3, Fig. 3). The marginal estimates of RR from IPW modeling are given in Table S6. The effect estimates of mortality risks associated with $PM_{2.5}$ vs. O_3 was very different across different causes of deaths (shown on the y-axis, Fig. 3). Table 3 shows the marginal estimates of the lag-effect accounted for a percentage increase in adjusted mortality risk (and 95%

CI) for cause-specific deaths for 10 units change in $PM_{2.5}$, O_3, or NO_2 exposure-accordingly, AP has affected both males and females. In the assessed age groups, patients aged under 65 (*i.e.*, <65 Y) were the most susceptible to AP effect with some exceptions wherein 65 and older age group showed relatively more at risk. Moreover, the higher RRs were associated with winter season as compared to the other seasons in general plausibly relating to the fact that the air quality remains very poor across northern India over a period of five months from Oct–Feb (represented in this study as winter season). In sharp contrast, the air quality during monsoon season (represented herein as other seasons) remains relatively clean as compared to the winter or summer seasons (Table 2). Overall, the AP was lower during other seasons [$PM_{2.5}$ varied from 17.7–95.6 μg m^{-3}, O_3 varied from 5.6–65.1 ppb, and NO_2 from 5.9–73.6 ppb] as compared to the rest of the seasons. However, it is worthwhile mentioning that in this study some of the cause-specific death risks were found to have causal linkage with AP not only in the winter season but also during summer and other seasons (Table 3). Our results on IPW causal inference are in line with previous studies documenting/discussing that the burden of disease and percent of deaths associated with the AP across India particularly in the northern region are substantially higher during winters. Some of the RRs were found to be significant for east UP whereas other RRs were significant for west Bihar, but these need to be further evaluated. One of the most plausible explanations for null findings in west Bihar vs. east UP may be due to exposure misclassification, since east UP includes all the patients who either live in Varanasi or are relatively near to the monitoring site as compared to west Bihar.

Fig. 4 shows the exposure-response (E-R) relationships between $PM_{2.5}$, O_3, and NO_2 for the assessed cause-specific mortality risks. The minimum daily $PM_{2.5}$ concentration of 17.7 μg m^{-3} was observed during summer as well as in other seasons (monsoon, Table 2) when uplifted mineral dust represents one of the major sources of ambient aerosols over the IGP (mineral dust contributes ≈37% of the ambient $PM_{2.5}$) (Rajeev *et al*., 2018). The minimum daily O_3 concentration of 5.6 ppb was observed during winter as well as in other seasons (monsoon, Table 2).

Now we would like to explain more about causation (Hernán and Robins, 2020). Causal modeling seeks to manipulate observational studies to make them look like randomized controlled trials, by making the exposure of interest independent of the potential confounders (Hernán and Robins, 2020). Trials balance the distribution of covariates between exposed and unexposed. Generalized Propensity Scores (GPS) are a way to mimic that because they are a balancing score (Qiu *et al*., 2020). The balance scores from the current IPW causal modeling are shown in Fig. 5; the scores for each of the covariates lie within a suggested range of ±0.2. Thus, it can be translated as conditional on score, the distribution of observed covariates should be the same between exposed and unexposed.

We want to look at the distribution of cause-specific deaths in the population. So, we would like to know what it looks like in different sub-groups (by age, sex, region, season, etc.). So, the first assertion here would be like is there a large enough sample to understand the distribution? In other words, are the samples a good representative of the population under study? So, how do we compute the distribution in the population with a non-representative sample if we have a missing data problem—which is broadly the case in the health records? To solve/address this assertion of missing health record or sampling bias, we can determine the weight and apply it to return to a representative sample of the whole population. We weight each observation by 1/probability of being selected. So, by weighting, we are assuming that conditional on sub-groups, people are missing at random and hence exchangeable. So, in the beginning the issue was that the exposure can be correlated with some other variables. However, if we randomly assign exposure then it is reasonable to think that there is no confounding. So, if we can solve the missing data problem, we have a causal model and that is what the inverse probability weighting (IPW) does. In this study, we have applied inverse probability weighting (IPW) causal modeling to obtain marginal effect estimates.

So, by applying appropriate weight in the analysis, we seek to achieve exposure independent of the confounders, measured or unmeasured. However, unmeasured confounders can still affect the estimated weights and may lead to biased results. In this context, the E-value has been used as a tool to characterize robustness to unmeasured confounding (VanderWeele and Ding, 2017). Sensitivity analysis using the E-value has been used to provide a measurement of how strong an unobserved confounder should be to explain away the observed associations. For example, in overall case of in-hospital all-cause deaths linked with exposure to $PM_{2.5}$, with an observed mortality risk of 1.0176, an unmeasured confounder that was associated with both the outcome and the exposure by a mortality risk of 1.15-fold each, above and beyond the measured confounders, could explain away the estimate, but weaker confounding could not (Table S7); to move the confidence interval to include the null, an unmeasured confounder that was associated with the outcome and the exposure by a mortality risk of 1.14-fold each could do so, but weaker confounding could not (Table S7). Likewise, the interpretation of robustness to

unmeasured confounding for each one of the RR values reported in Table S7 can be made. In view of unavailability of uncertainty values in air pollution measurements (from the CPCB) and to address spatial variability across the study region (east UP and west Bihar), we have investigated the literature and found that a recent study (Brown *et al*., 2022) showed ~ 30% spatial variability in annual ambient $PM_{2.5}$ concentrations over east UP-west Bihar region. We have already discussed results from causal modeling from a single monitoring station (in Varanasi, Table 3 & Table S6). We have further carried out a sensitivity analysis wherein imposed an overall ±30% shift in the distribution of each of the air pollutants ($PM_{2.5}$, O_3, and NO_2; Table S8) and performed the causal modeling with these datasets. The results of this sensitivity analysis are given in supplemental information (Table S2). Our results from this sensitivity analysis suggest that shifting the air pollution concentrations by 30% though changes the health effects estimates (Table S2 vs. Table 3) quantitatively but not qualitatively (except for a couple of effect estimates only). Thus, our causal inference on linkage of air pollution and different health outcomes along with the sensitivity analysis performed for ±30% shift is air pollution distribution, documents the relative risk estimates of cause-specific mortalities occurring due to ambient air pollution in the Indo-Gangetic Plain (covering east UP-west Bihar region). We have applied the causal modeling to local datasets from Indian region and all the relative risk estimates from this study are novel. Furthermore, the results given in the supplemental information from the association modeling (Tables S3, S4, S9, S10 and Fig S6, Fig S7, Fig S8) show a huge difference when compared with the IPW modeling results and could be attributable to influence of selection bias in the previous one. However, the marginal estimates shown in this work based on the IPW causal modeling seeks to minimize/remove the influence of selection bias. Probably this suggests that causal modeling provides a more robust effect estimate as compared to the simple association modeling, as suggested by several previous studies. A summary of major findings from this study is shown in Fig 6. It is worthwhile mentioning that, in view of very limited studies on AP and public health in India, there is a high-level need for conducting a long-term study of air pollution & public health research across the nation (Adar and Pant, 2022).

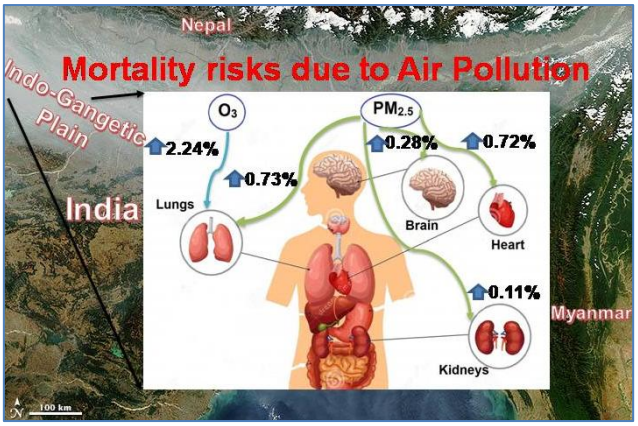

Fig. 6. Summarizing major findings of this study on non-accidental premature cause-specific mortality risks attributable to AP from causal modeling in a subset of Indian population

3.1. *Discussion*

AP is among the world's biggest human health risks which is responsible for ~7 million premature non-accidental deaths annually (IQAir, 2021). AP, representing among the top risk factors for premature deaths in South Asia, is responsible for ~11% of all-cause deaths (non - accidental) and 40 million disability-adjusted life years (IQAir, 2021). In this study, we have investigated causations between $PM_{2.5}$, O_3, and NO_2 exposures and cause-specific mortalities for the period 2012–2018. The dataset on health outcomes (i.e., cause-specific mortalities) were limited to an area covering east UP and west Bihar regions—both UP and Bihar states are situated in northern India within the IGP. A recent study revealed that around 1.24 million premature deaths occur annually in India, of which 21% (= 0.26 million) and 7.8% (= 0.096 million) have been suggested from the states of Uttar Pradesh (UP) and Bihar, respectively, can be averted by reducing the AP substantially through sensitization and inter-sectoral interventions (Balakrishnan *et al*., 2019). It is worthwhile mentioning that previous researchers from elsewhere have found a strong base of evidence for mortality risks at even low levels of $PM_{2.5}$ exposure (Papadogeorgou *et al*., 2019). However, the regions marked with high air pollution need much more attention as far as the health co-benefits point of view is concerned. Summing up, in this study, after adjusting for time trends, weather parameters, and incorporating co-pollutants and their lag effects, the adjusted cause-specific mortality risks were found to be significantly linked with $PM_{2.5}$, and O_3.

Now we would like to discuss plausible biological mechanisms pertaining to AP and cause-specific mortalities. Particulate matter pollution has been associated with several cardiovascular health effects including mortality and hospital admissions as well as autonomic dysfunction and inflammation (Dockery *et al*., 1993; Pope *et al*., 2004; Pope and Dockery, 2006; Schwartz, 1998; Schwartz *et al*., 2005). PM from vehicular emissions were found to have greater effect on inflammatory markers whereas acute effect of O_3 exposure was observed as a decrease in forced expiratory

volume (FEV1) (Alexeeff *et al*., 2007; Zeka *et al*., 2006). Short-term increases in ambient PM are thought to increase the risk of cardiovascular events by a combination of at least four separate but related mechanisms. Firstly, PM-related changes in autonomic nervous system activity, as assessed by the heart-rate variability, have been observed in experimental animals and in human panel studies (Gold *et al*., 2000; Liao D *et al*., 1999; Pope *et al*., 1999). Results from these studies are consistent with sympathetic activation or reduction of parasympathetic (vagal) tone following exposure to PM. Secondly, PM-related changes in hematological parameters have been reported, including decreased red blood cell indices, increased blood viscosity, and enhanced peripheral arterial thrombosis (Nemmar *et al*., 2003; Peters *et al*., 1997). Thirdly, there is evidence that short-term exposure to PM can induce an acute systemic inflammatory response with an increased number of circulating neutrophils and increased levels of C-reactive protein (Eeden and Hogg, 2002; Peters *et al*., 2001). Fourthly, short-term exposure to ambient PM can promote endothelial cell injury and impair endothelial cell function, as evidenced by PM-related increases in plasma markers of endothelial injury, changes in systemic hemodynamics, impaired endothelium-dependent vasodilation, and reduced brachial artery diameter (Barregard *et al*., 2006; Brook *et al*., 2002; Van Hee *et al*., 2009). These findings suggest that autonomic, hemostatic, inflammatory, and endothelial disturbances with consequent changes in cardiac and vascular functions may underline the particulate-related increased risk of cardiovascular events.

It has been reported earlier from a previous research on 31 subjects with heart failure that oxygen saturation by pulse oximetry was inversely associated with concentrations of $PM_{2.5}$, O_3 and SO_2, whereas heart rate was found to be increased with the $PM_{2.5}$, NO_2, and SO_2. In this same group of subjects, increased concurrent day ozone levels predicted poorer self-perceived general health (Goldberg *et al*., 2009, 2008). Importantly, in a separate study, it was reported that blood levels of B-type natriuretic peptide (BNP, a heart failure biomarker that correlates with filling pressure) in subjects with chronic heart failure were substantially variable and not associated with any pollutants, including $PM_{2.5}$, CO, O_3, SO_2, NO_2, and black carbon (Wellenius *et al*., 2007). Overall, these studies suggested that symptoms and functional status in subjects with heart failure can be influenced by short-term variations in ambient AP. However, this effect was not reliably detected by the changes in circulating BNP. O_3 is a potent oxidizing agent that reacts rapidly upon contact with various substances, including those present in living tissues. At higher concentrations, it rapidly produces cell death, and at lower concentrations, it damages proteins, lipids (*e.g*., in cell membranes), and a variety of important biomolecules (*e.g*., those in mucus, pulmonary surfactant, and the interior cells). As a result, at various concentrations O_3 can produce a range of potentially adverse health effects.

Atmospheric aerosols, made up of several species and molecular moieties, can have variation in size, chemical composition, surface area, and mass concentrations as a function of its sources, surface reactivity and chemical reactions of its precursors, space, and time (Bhandari *et al*., 2020; Brook *et al*., 2004; Limaye *et al*., 2022; Rajput and Gupta, 2020). A growing body of evidence suggests an association between smaller particle sizes and larger adverse cardiopulmonary effects. For example, ultrafine particles (UFPs, < 100 nm), are capable to catalyze the production of reactive oxygen species (ROS), leading to pro-oxidative and proinflammatory effects in the lungs and cardiovascular system. Diesel particulate matter (DPM) pro-oxidant effects have been ascribed to their aromatic and polar constituents as these fractions have been shown to be the most active in the induction of antioxidant genes such as heme oxygenase 1 (HO-1), glutathione S-transferase (GST) and other phase-II enzymes that offer protection against oxidative stress in macrophages and epithelial cells (Li *et al*., 2004). This line of antioxidant defense is regulated by the transcription factor p45-NFE2 related transcription factor 2 (Nrf2) via modulation of its proteasomal degradation in the cytosol and translocation into the nucleus (Li *et al*., 2004). Likewise, the redox potential of ambient PM and its ability to trigger Nrf2-regulated genes vary significantly among particles of different sizes, partly due to its different content of pro-oxidative and electrophilic chemicals. UFPs have been shown to exhibit greater redox potential than larger particles (Li *et al*., 2003); UFP larger pro-oxidative effects are associated with their greater content of PM organic carbon and polycyclic aromatic hydrocarbons (PAHs), suggesting a role for these organic substances in generating redox activity (Ayres *et al*., 2008; Ntziachristos *et al*., 2007). Also, previous researchers have found positive associations of outdoor quasi-ultrafine $PM_{0.25}$ (< 0.25 micron) with biomarkers of systemic inflammation such as interleukin (IL-6), soluble tumor necrosis factor receptor II (sTNF-RII) and C-reactive protein (CRP) (Delfino, R. J. *et al*., 2009, 2008).

The current study has been conducted during the period from Jan 01, 2012, to Dec 31, 2018, whereas a previous study (Singh *et al*., 2021), was performed for the period Jan 01, 2009, to Dec 31, 2016. The previous study investigated the association between acute exposure to AP and all-cause mortality for Varanasi (Singh *et al*., 2021). In view of non-availability of SES data, the previous study

has considered institutional and non-institutional deaths as a proxy for SES (Singh *et al*., 2021). However, it is a general realization that if any subject/patient started feeling uneasiness suddenly and died before reaching to the hospital then his or her death will be recorded as a non-institutional death and which is a misclassification. So, information on education, lagged income, and fertility should be considered as the more reliable proxies for SES. The previous study has reported the mean percent increase in adjusted all-cause mortality risk of 1.51 (95% CI: 0.71–2.31) for every 10-units change in $PM_{2.5}$ exposure (Singh *et al*., 2021). In the current study, it is evident from Table 3 that for every 10-units change in $PM_{2.5}$ exposure, the mean percent increase in adjusted mortality risk was 1.76 (95% CI: 1.57–1.95) for in-hospital all-cause deaths, 0.28 (95% CI: 0.07–0.50) for neurological deaths, 0.73 (95% CI: 0.47–0.98) for respiratory deaths, 0.72 (95% CI: 0.48–0.96) for cardiovascular deaths, and 0.11 (95% CI: 0.09–0.14) for nephrological deaths. So, in a nutshell, the current study finds that the mean percent increase in death risks due to $PM_{2.5}$ for certain causes like respiratory and cardiovascular deaths is relatively high as compared to neurological and nephrological death risks. Furthermore, though the mean percent increase in the in-hospital all-cause death risk (both mean and 95% CI: 1.76; 1.57–1.95) in the current study for every 10-units change in $PM_{2.5}$ exposure looks somewhat higher as compared to the mean percent increase in all-cause mortality (1.51; 95% CI: 0.71–2.31) estimates reported from association modeling in a previous study (Singh *et al*., 2021), but the CIs have a good length of overlap. Likewise, though mortality risk due to O_3 was significant for all the studied causes-specific deaths but was maximum for the respiratory deaths while NO_2 showed only causal linkage with cardiovascular deaths.

Associations between short-term exposure to $PM_{2.5}$ and cardiovascular deaths as well as respiratory deaths are well established, for example (Orellano *et al*., 2020). Accordingly, a 10 μg m^{-3} increase in $PM_{2.5}$ was found to be associated with 0.92% (95% CI: 0.61, 1.23) increase and 0.73% (95% CI: 0.29, 1.16) increase in cardiovascular and respiratory death risks, respectively (Orellano *et al*., 2020). Based on the IPW causal modeling in this study (a 3-pollutants model and with cumulative lag effects), we found a quite similar marginal estimate linking a 10 μg m^{-3} increase in short-term exposure to $PM_{2.5}$ to be associated with 0.72% (95% CI: 0.48, 0.96) increase and 0.73% (95% CI: 0.47, 0.98) increase in cardiovascular and respiratory death risks, respectively. The previous systematic literature review and meta-analysis (Orellano *et al*., 2020), mainly focused on China, the USA, and Europe with single lags but has no study included from the Indian region on AP and cause-specific deaths; showing a dearth of information on AP and cause-specific mortality analysis from the Indian region. A recent study, conducted among hemodialysis patients (a nephrological disease) in the USA, has reported that a 10 μg m^{-3} increase in short-term exposure to $PM_{2.5}$ from wildfire was associated with 4.0% (95% CI: 1.0, 7.0) increase in the same-day mortality (Xi *et al*., 2020). A previous study, focusing on Alzheimer's disease development (a neurological disease) due to AP in Mexico City, has reported many combustion-derived nanoparticles in the brain of urban subjects (González-Maciel *et al*., 2017). Furthermore, researchers now recognize a strong connection between the ingested particles in gut microbiome and indirect neurological effects (Peeples, 2020). An earlier study has found that a 10 μg m^{-3} increase in short-term exposure to $PM_{2.5}$ was associated with a 1.1% (95% CI: 1.1, 1.2) increase in mortality risk from stroke whereas the association with O_3 was statistically non-significant (Shah *et al*., 2015). Our results from the IPW causal modeling (Table 3 and Table S6), exhibited a near similar feature that every 10 μg m^{-3} increase in short-term exposure to $PM_{2.5}$ is linked with a 0.28% (95% CI: 0.07, 0.50) increase in neurological death risk whereas for O_3 it showed a 0.72% (95% CI: 0.51, 0.93) increase.

This study assesses the adjusted mortality risks, for four different cause-specific deaths, associated with AP ($PM_{2.5}$, O_3, and NO_2) after controlling the weather, and time-trends and accounting for the lag effect and applied the IPW causal modeling. Yet, this study has some limitations. Firstly, though we have a 7-Y (2012–2018) ground-based time-series of exposure variables (air pollution) but the measurements are available from only one receptor location in Varanasi. Due to this very reason, our study assumes the same daily average exposure to AP for every person residing in east UP and west Bihar region on a given day of a year. This assumption might have led to exposure misclassification of AP. Of the four assumptions of IPW estimation, the consistency refers to the exposure being sufficiently well defined (Igelström *et al*., 2022); this assumption is broken when source-contributions of air pollution are different across the study region. Next, the assumption of non-interference requires that an individual's exposure is not affected by the exposure status of anyone else. This assumption is also not fulfilled in the analytical framework, as exposure is similar for people in the same place at the same time. The utilization of high-resolution data sets, in future studies, will reduce exposure uncertainty. Thus, we urge through this study to all concerned stakeholders to enhance the number of ground-based AP monitoring stations across the Indian region for a more accurate validation and bias correction of AI/ML models. Another major limitation is the lack of additional information on subjects like their socio-economic status (SES), diet, smoking, etc. Even so, our study presents novel information, based on IPW

causal modeling, on the linkage between cause-specific mortality risks of neurological, respiratory, cardiovascular, nephrological deaths and the in-hospital all-cause deaths and short-term exposure to AP in the IGP. A recent study applied instrumental variable analysis causal modeling approach to assess the short-term exposure to ambient $PM_{2.5}$ and all-cause mortality across ten Indian cities (de Bont *et al*., 2024). Previous studies from India have reported mainly on the all-cause mortality risks due to AP while a couple of studies focused on cardiovascular abdeaths. Current findings, from causal modeling over east UP-west Bihar region could serve as a baseline information of short-term exposure to AP and cause-specific mortalities from a subset of Indian population. This can eventually help all concerned stakeholders to prepare an effective policy including both adaptation and mitigation strategies and its proper implementation for a better air quality over the Indian region particularly across northern India.

4. Conclusions

Summing up, the northern part of India has been witnessing a severe AP for decades. By analyzing 7-year of local health record & AP data in the IGP region, this study provided evidence on the strong causation between AP ($PM_{2.5}$, O_3, and NO_2) and cause-specific mortalities. A recent study from India (Brown *et al*., 2022), using a single pollutant model has reported significant associations between long-term exposure to increase by every 10-units of $PM_{2.5}$ and percent increase in chronic stroke (neurological death risk; 9% [95% CI: 4, 14]) and all-cause mortality risks (2% [95% CI: 1, 3]). Effect modifications due to sex (M, F), age (<65, ≥ 65), season (winter: Oct–Feb; summer: Mar–May; other seasons: June–Sept), and region (east UP, west Bihar) have also been analyzed in this study. The lag effect of AP significant up to 6 days has been observed. The vulnerability, of both males and females, <65 and 65 and older population, throughout the year but more pronounced in winters, due to $PM_{2.5}$ and O_3 was found. The current findings can be used as evidence, in conjunction with the preexisting literature, by the stakeholders in developing appropriate adaptation and mitigation policies to achieve clean air for all at the earliest possible. Future research in observational epidemiology focusing on a larger dataset of spatially and temporally resolved air pollution (co-pollutants) and cause-specific mortalities across the Indian region is warranted.

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Data Availability Statement

We have provided all relevant data summary, of AP and health outcomes, in the form of tables and Figs in the main manuscript as well as in the supplemental information. Data of AP can be accessed from the India's Central Pollution Control Board open access website (https://app.cpcbccr.com/ccr/#/caaqm-dashboard-all/ caaqm - landing). The hospital mortality records are not accessible to the public due to national policies of data in India. Further queries, if any, on data availability can be redirected to the corresponding author.

Software Availability Statement

In the current study, modeling has been carried out using R which is an open source and can be installed from: https://support--rstudiocom.netlify.app/products/rstudio /download/.

Author's contribution

PR: Conceptualization, Data curation, Investigation, Methodology, Validation, Writing - original draft and revision. (*email: prajput.prl@gmail.com*).
RKM: Conceptualization, Methodology, Supervision, Funding acquisition, Project administration, Writing-review & editing, and revision. (*email: rkmall@bhu.ac.in*).
NS: Conceptualization, Data curation, Methodology, Writing - review & editing, and revision. (*email: nidhirocks.nidhi4@gmail.com*).
RP: Conceptualization, Data curation, Methodology, Writing - review & editing, and revision. (*email: rajnitip@bhu.ac.in*).

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References

Adar S D and Pant P, 2022, "Invited Perspective: Forward Progress in Characterizing the Mortality Burden of PM2.5 for India", *Environ. Health Perspect.* **130** 091303-1-2, doi: https://doi.org/10.1289/EHP10979 .

Alexeeff S E, Litonjua A A, Suh H, Sparrow D, Vokonas P S and Schwartz J, 2007, "Ozone Exposure and Lung Function: Effect Modified by Obesity and Airways Hyperresponsiveness in the VA Normative Aging Study", *Chest* **132** 1890–1897, https://doi.org/10.1378/chest.07-1126.

Apte J S, Marshall J D, Cohen A J and Brauer M, 2015, "Addressing Global Mortality from Ambient PM2.5", *Environ. Sci. Technol.* **49** 8057–8066, https://doi.org/10.1021/acs.est.5b01236.

Ayres J G, Borm P, Cassee F R, Castranova V, Donaldson K, Ghio A, Harrison R M, Hider R, Kelly F, Kooter I M, Marano F, Maynard R L, Mudway I, Nel A, Sioutas C, Smith S, Baeza-Squiban A, Cho A, Duggan S and Froines J, 2008, "Evaluating the Toxicity of Airborne Particulate Matter and Nanoparticles by Measuring Oxidative Stress Potential—A Workshop Report and Consensus Statement", *Inhal. Toxicol.* **20** 75–99, https://doi.org/10.1080/08958370701665517.

Balakrishnan K, Dey S, Gupta T, Dhaliwal R S, Brauer M, Cohen A J, Stanaway J D, Beig G, Joshi T K, Aggarwal A N, Sabde Y, Sadhu H, Frostad J, Causey K, Godwin W, Shukla D K, Kumar G A, Varghese C M, Muraleedharan P, Agrawal A, Anjana R M, Bhansali A, Bhardwaj D, Burkart K, Cercy K, Chakma J K, Chowdhury S, Christopher D J, Dutta E, Furtado M, Ghosh S, Ghoshal A G, Glenn S D, Guleria R, Gupta R, Jeemon P, Kant R, Kant S, Kaur T, Koul P A, Krish V, Krishna B, Larson S L, Madhipatla K, Mahesh P A, Mohan V, Mukhopadhyay S, Mutreja P, Naik N, Nair S, Nguyen G, Odell C M, Pandian J D, Prabhakaran D, Prabhakaran P, Roy A, Salvi S, Sambandam S, Saraf D, Sharma M, Shrivastava A, Singh V, Tandon N, Thomas N J, Torre A, Xavier D, Yadav G, Singh S, Shekhar C, Vos T, Dandona R, Reddy K S, Lim S S, Murray C J L, Venkatesh S and Dandona L, 2019, "The impact of air pollution on deaths, disease burden, and life expectancy across the states of India: the Global Burden of Disease Study 2017", *Lancet Planet. Health* **3** e26–e39, https://doi.org/10.1016/S2542-5196(18)30261-4.

Barregard L, Sällsten G, Gustafson P, Andersson L, Johansson L, Basu S and Stigendal L, 2006, "Experimental Exposure to Wood-Smoke Particles in Healthy Humans: Effects on Markers of Inflammation, Coagulation, and Lipid Peroxidation", *Inhal. Toxicol.* **18** 845–853, https://doi.org/10.1080/08958370600685798.

Bhandari S, Gani S, Patel K, Wang D S, Soni P, Arub Z, Habib G, Apte J S and Hildebrandt R L, 2020, "Sources and atmospheric dynamics of organic aerosol in New Delhi, India: insights from receptor modeling", *Atmos. Chem. Phys.* **20** 735–752, https://doi.org/10.5194/acp-20-735-2020.

Brook R D, Brook J R, Urch B, Vincent R, Rajagopalan S and Silverman F, 2002, "Inhalation of Fine Particulate Air Pollution and Ozone Causes Acute Arterial Vasoconstriction in Healthy Adults", *Circulation* **105** 1534–1536, https://doi.org/10.1161/01.CIR.0000013838.94747.64.

Brook R D, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, Luepker R, Mittleman M, Samet J, Smith S C and Tager I, 2004, "Air Pollution and Cardiovascular Disease", *Circulation* **109** 2655–2671, https://doi.org/10.1161/01.CIR.0000128587.30041.C8.

Brown P, Izawa Y, Balakrishnan K, Fu Sze H, Chakma J, Menon G, Dikshit R, Dhaliwal R S, Rodriguez P S, Huang G, Begum R, Hu H, D'Souza G, Guleria R and Jha P, 2022, "Mortality Associated with Ambient PM2.5 Exposure in India: Results from the Million Death Study", *Environ. Health Perspect.* **130** 097004, https://doi.org/10.1289/EHP9538.

Census 2011 Census of India, "Ministry of Home Affairs, Government of India", https://www.censusindia.gov.in/2011census/population_enumeration.html.

Choudhary R K, Joshi P, Ghosh S, Ganguly D, Singh N, Mall R K, & Dey S, 2024, "Excess Mortality Risk Due to Heat Stress in Different Climatic Zones of India", *Env. Sci. & Technology*. **58(1),** 342-351https://doi.org/10.1021/acs.est.3c05218.

Cohen A J, Ross A H, Ostro B, Pandey K D, Krzyzanowski M, Künzli N, Gutschmidt K, Pope A, Romieu I, Samet J M and Smith K, 2005, "The Global Burden of Disease Due to Outdoor Air Pollution", *J. Toxicol. Environ. Health Part A* **68** 1301–1307, https://doi.org/10.1080/15287390590936166.

Cole S R and Hernán M A, 2008, "Constructing Inverse Probability Weights for Marginal Structural Models", *Am. J. Epidemiol.* **168** 656–664, https://doi.org/10.1093/aje/kwn164.

CPCB 2021 Central Pollution Control Board of India; https://cpcb.nic.in/.

CREA 2020 Center for Research on Energy and Clean Air (CREA) 2020, "Quantifying the economic costs of air pollution from fossil fuels", https://energyandcleanair.org/wp/wp-content/uploads/2020/02/Cost-of-fossil-fuels-briefing.pdf.

Delfino R J, Staimer N, Tjoa T, Gillen D L, Polidori A, Arhami M, Kleinman M T, Vaziri N D, Longhurst J and Sioutas C, 2009, "Air Pollution Exposures and Circulating Biomarkers of Effect in a Susceptible Population: Clues to Potential Causal Component mixtures and mechanisms", *Environ. Health Perspect.* **117** 1232–1238, https://doi.org/10.1289/ehp.0800194.

Delfino R J, Staimer N, Tjoa T, Polidori A, Arhami M, Gillen D L, Kleinman M T, Vaziri N D, Longhurst J, Zaldivar F and Sioutas C, 2008, "Circulating Biomarkers of Inflammation, Antioxidant Activity, and Platelet Activation Are Associated with Primary Combustion Aerosols in Subjects with Coronary Artery Disease", *Environ. Health Perspect.* **116** 898–906, https://doi.org/10.1289/ehp.11189.

de Bont J, Krishna B, Stafoggia M, Banerjee T, Dholakia H, Garg A, Ingole V, Jaganathan S, Kloog I, Lane K, Mall R K, Mandal S, Nori-Sarma A, Prabhakaran D, Rajiva A, Tiwari A S, Wei Y, Wellenius G A, Schwartz J, Prabhakaran P and Ljungman P, 2024, "Ambient air pollution and daily mortality in ten cities of India: a causal modelling study", Lancet Planet. Health **8** e433–e440, https://doi.org/10.1016/S2542-5196(24)00114-1.

de Bont, J de, Rajiva A, Mandal S, Banerjee T, Dholakia H, R K Mall,... & Ljungman P. 2025, "Synergistic associations of ambient air pollution and heat on daily mortalit y in India". Environment International, 199, 109426. https://doi.org/10.1016/j.envint.2025.109426.

Di Q, Dai L, Wang Y, Zanobetti A, Choirat C, Schwartz J D and Dominici F, 2017, "Association of Short-term Exposure to Air Pollution With Mortality in Older Adults", JAMA **318** 2446–2456, https://doi.org/10.1001/jama.2017.17923.

Dockery D, Pope C 3rd, Xu X, Spengler J D, Ware J H, Fay M E, Ferris Jr B G and Speizer F E, 1993, "An association between air pollution and mortality in six U.S. cities", *N Engl J Med.* **329** 1753–1759.

Dutta P, Rajput P, Mukherjee P, Madan P and Mavalankar D, 2022, "A Successful Heat Wave Prevention in Ahmedabad Calls for Segregated Health Record: Highlights from Existing Heat Action Plan", *Aerosol Air Qual. Res.* **22** 220300, https://doi.org/10.4209/aaqr.220300.

Eeden S F. van and Hogg J C, 2002, "SYSTEMIC INFLAMMATORY RESPONSE INDUCED BY PARTICULATE MATTER AIR POLLUTION: THE IMPORTANCE OF BONE-MARROW STIMULATION", *J. Toxicol. Environ. Health Part A* **65** 1597–1613, https://doi.org/10.1080/00984100290071685.

Gasparrini A, 2011, "Distributed Lag Linear and Non-Linear Models in R: The Package dlnm", *J. Stat. Softw.* **43** 1–20.

George, F., Joshi, P., Dey, S., Mall, R. K., & Ghosh, S. 2025. "A framework for city-specific air quality health index: a comparative assessment of Delhi and Varanasi, India". *Environmental Research Letters*, **20** (8) 084067. https://doi.org/10.1088/1748-9326/aded26.

Gold D R, Litonjua A, Schwartz J, Lovett E, Larson A, Nearing B, Allen G, Verrier M, Cherry R and Verrier R, 2000, "Ambient Pollution and Heart Rate Variability", *Circulation* **101** 1267–1273; https://doi.org/10.1161/01.CIR.101.11.1267.

Goldberg M S, Giannetti N, Burnett R T, Mayo N E, Valois M -F and Brophy J M, 2009, "Shortness of breath at night and health status in congestive heart failure: Effects of environmental conditions and health-related and dietary factors", *Environ. Res.* **109** 166–174, https://doi.org/10.1016/j.envres.2008.10.007.

Goldberg M S, Giannetti N, Burnett R T, Mayo N E, Valois M -F and Brophy J M, 2008, "A panel study in congestive heart failure to estimate the short-term effects from personal factors and environmental conditions on oxygen saturation and pulse rate", *Occup. Environ. Med.* **65** 659, https://doi.org/10.1136/oem.2007.034934.

González-Maciel A, Reynoso-Robles R, Torres-Jardón R, Mukherjee P S and Calderón-Garcidueñas L, 2017, "Combustion-Derived Nanoparticles in Key Brain Target Cells and Organelles in Young Urbanites: Culprit Hidden in Plain Sight in Alzheimer's Disease Development", *J. Alzheimers Dis.* **59** 189–208, https://doi.org/doi: 10.3233/JAD-170012. PMID: 28598844.

Hernán M A and Robins J M, 2020, "Causal Inference: What If", Boca Raton: Chapman & Hall/CRC.

Igelström E, Craig P, Lewsey J, Lynch J, Pearce A and Katikireddi S V, 2022, "Causal inference and effect estimation using observational data", *J. Epidemiol. Community Health* **76** 960, https://doi.org/10.1136/jech-2022-219267.

IQAir, 2021, "World Air Quality Report, Region & City PM2.5 Ranking".

Jethva H, Torres O, Field R D, Lyapustin A, Gautam R and Kayetha V, 2019, "Connecting Crop Productivity, Residue Fires, and Air Quality over Northern India", *Sci. Rep.* **9** 16594, https://doi.org/10.1038/s41598-019-52799-x.

Kloog I, Ridgway B, Koutrakis P, Coull B A and Schwartz J D, 2013, "Long- and short-term exposure to PM2.5 and mortality: using novel exposure models", *Epidemiology* **24** 555–561, https://doi.org/10.1097/EDE.0b013e318294beaa.

Krishna B, Mandal S, Madhipatla K, Reddy K S, Prabhakaran D and Schwartz J D, 2021, "Daily nonaccidental mortality associated with short-term PM2.5 exposures in Delhi, India", *Environ. Epidemiol.* 5(4):e167 https://doi.org/10.1097/EE9.0000000000000167 .

Lelieveld J, Evans J S, Fnais M, Giannadaki D and Pozzer A, 2015, "The contribution of outdoor air pollution sources to premature mortality on a global scale", *Nature* **525** 367–371, https://doi.org/10.1038/nature15371.

Li N, Alam J, Venkatesan M I, Eiguren-Fernandez A, Schmitz D, Di Stefano E, Slaughter N, Killeen E, Wang X, Huang A, Wang M, Miguel A H, Cho A, Sioutas C and Nel A E, 2004, "Nrf2 Is a Key Transcription Factor That Regulates Antioxidant Defense in Macrophages and Epithelial Cells: Protecting against the Proinflammatory and Oxidizing Effects of Diesel Exhaust Chemicals1", *J. Immunol.* **173** 3467–3481, https://doi.org/10.4049/jimmunol.173.5.3467.

Li N, Sioutas C, Cho A, Schmitz D, Misra C, Sempf J, Wang M, Oberley T, Froines J and Nel A, 2003, "Ultrafine Particulate Pollutants Induce Oxidative Stress and Mitochondrial Damage", *Environ. Health Perspect.* **111**, 455–460.

Liao D, Creason J, Shy C, Williams R, Watts R and Zweidinger R, 1999, "Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly", *Environ. Health Perspect.* **107** 521–525, https://doi.org/10.1289/ehp.99107521.

Limaye V S, Magal A, Joshi J, Maji S, Dutta P, Rajput P, Pingle S, Madan P, Mukerjee P, Bano S, Beig G, Mavalankar D, Jaiswal A and Knowlton K, 2022, "Air quality and health co-benefits of climate change mitigation and adaptation actions by 2030: an interdisciplinary modeling study in Ahmedabad, India", *Environ. Res.: Health* https://doi.org/10.1088/2752-5309/aca7d8.

Morawska L, Zhu T, Liu N, Amouei Torkmahalleh M, de Fatima Andrade M, Barratt B, Broomandi P, Buonanno G, Carlos Belalcazar Ceron L, Chen J, Cheng Y, Evans G, Gavidia M, Guo H, Hanigan I, Hu M, Jeong C H, Kelly F, Gallardo L, Kumar P, Lyu X, Mullins B J, Nordstrøm C, Pereira G, Querol X, Yezid Rojas Roa N, Russell A, Thompson H, Wang H, Wang L, Wang T, Wierzbicka A, Xue T and Ye C, 2021, "The state of science on severe air pollution episodes: Quantitative and qualitative analysis", *Environ. Int.* **156** 106732, https://doi.org/10.1016/j.envint.2021.106732.

Nemmar A, Hoet P H M, Dinsdale D, Vermylen J, Hoylaerts M F and Nemery B, 2003, "Diesel Exhaust Particles in Lung Acutely Enhance Experimental Peripheral Thrombosis", *Circulation* **107** 1202–1208, https://doi.org/10.1161/01.CIR.0000053568.13058.67.

Nori-Sarma A, Gurung A, Azhar G S, Rajiva A, Mavalankar D, Sheffield P and Bell M L, 2017, "Opportunities and Challenges in Public Health Data Collection in Southern Asia: Examples from Western India and Kathmandu Valley, Nepal", *Sustainability* **9** https://doi.org/10.3390/su9071106.

Ntziachristos L, Froines J R, Cho A K and Sioutas C, 2007, "Relationship between redox activity and chemical speciation of size-fractionated particulate matter", *Part. Fibre Toxicol.* **4** 5. https://doi.org/10.1186/1743-8977-4-5.

Orellano P, Reynoso J, Quaranta N, Bardach A and Ciapponi A, 2020, "Short-term exposure to particulate matter (PM10 and PM2.5), nitrogen dioxide (NO2), and ozone (O3) and all-cause and cause-specific mortality: Systematic review and meta-analysis", *Environ. Int.* **142** 105876, https://doi.org/10.1016/j.envint.2020.105876.

Papadogeorgou G, Kioumourtzoglou M -A, Braun D and Zanobetti A, 2019, "Low Levels of Air Pollution and Health: Effect Estimates, Methodological Challenges, and Future Directions", *Curr. Environ. Health Rep.* **6** 105–115, https://doi.org/10.1007/s40572-019-00235-7.

Peeples L, 2020, "News Feature: How air pollution threatens brain health", *Proc. Natl. Acad. Sci. USA* **117** 13856, https://doi.org/10.1073/pnas.2008940117.

Peters A, Döring A, Wichmann H -E and Koenig W, 1997, "Increased plasma viscosity during an air pollution episode: a link to mortality?", *Lancet* **349** 1582–1587, https://doi.org/10.1016/S0140-6736(97)01211-7.

Peters A, Fröhlich M, Döring A, Immervoll T, Wichmann H -E, Hutchinson W L, Pepys M B and Koenig W, 2001, "Particulate air pollution is associated with an acute phase response in men. Results from the MONICA–Augsburg Study", *Eur. Heart J.* **22** 1198–1204, https://doi.org/10.1053/euhj.2000.2483.

Phalen R F and Phalen R N, 2013, "Introduction to Air Pollution Science: A Public Health Perspective", Jones & Bartlett Learning.

Pope C A, Burnett R T, Thurston G D, Thun M J, Calle E E, Krewski D and Godleski J J, 2004, "Cardiovascular Mortality and Long-Term Exposure to Particulate Air Pollution", *Circulation* **109** 71–77, https://doi.org/10.1161/01.CIR.0000108927.80044.7F.

Pope C A and Dockery DW, 2006, "Health Effects of Fine Particulate Air Pollution: Lines that Connect", *J. Air Waste Manag. Assoc.* **56** 709–742, https://doi.org/10.1080/10473289.2006.10464485.

Pope C A, Verrier R L, Lovett E G, Larson A C, Raizenne M E, Kanner R E, Schwartz J, Villegas G M, Gold D R and Dockery D W, 1999, "Heart rate variability associated with particulate air pollution", *Am. Heart J.* **138** 890–899, https://doi.org/10.1016/S0002-8703(99)70014-1.

Qiu X, Wei Y, Wang Y, Di Q, Sofer T, Awad Y A and Schwartz J, 2020, "Inverse probability weighted distributed lag effects of short-term exposure to PM2.5 and ozone on CVD hospitalizations in New England Medicare participants - Exploring the causal effects", *Environ. Res.* **182** 109095, https://doi.org/10.1016/j.envres.2019.109095.

Rajeev P, Rajput P, Singh A K and Gupta T, 2018, "Study of temporal variability and mass closure of PM2.5 and its chemical constituents during weak south-west monsoon", *Atmos. Poll. Res.* **9** 864–870, https://doi.org/10.1016/j.apr.2018.02.008.

Rajput P and Gupta T, 2020, "Instrumental Variable Analysis in Atmospheric and Aerosol Chemistry", Front. Environ. Sci. **8** 267, https://doi.org/10.3389/fenvs.2020.566136.

Rajput P, Singh A K, Biswas K, Qadri A M and Gupta T, 2021, "Source Contribution of Firecrackers Burst vs. Long-Range Transport of Biomass Burning Emissions Over an Urban Background", Front. Sustain. Cities **2** 68, https://doi.org/10.3389/frsc.2020.622050.

Schwartz J, 1998, "Air Pollution and Hospital Admissions for Heart Disease in Eight US Counties", *Epidemiology* **9**.

Schwartz J, Litonjua A, Suh H, Verrier M, Zanobetti A, Syring M, Nearing B, Verrier R, Stone P, MacCallum G, Speizer F E and Gold D R, 2005, "Traffic related pollution and heart rate variability in a panel of elderly subjects", *Thorax* **60** 455–461, https://doi.org/10.1136/thx.2004.024836.

Shah A S V, Lee K K, McAllister D A, Hunter A, Nair H, Whiteley W, Langrish J P, Newby D E and Mills N L, 2015, "Short term exposure to air pollution and stroke: systematic review and meta-analysis", *BMJ* **350** h1295, https://doi.org/10.1136/bmj.h1295.

Shaw C, Rastogi N, Rathi A, Kumar S and Meena R, 2024, "Sources and processes affecting the abundances of atmospheric NHx using $\delta^{15}N$ over northwestern Indo-Gangetic plain", *Chemosphere* **359** 142356, https://doi.org/10.1016/j.chemosphere.2024.142356.

Singh N, Mhawish A, Banerjee T, Ghosh S, Singh R S and Mall R K, 2021a, "Association of aerosols, trace gases and black carbon with mortality in an urban pollution hotspot over central Indo-Gangetic Plain", *Atmos. Environ.* **246** 118088, https://doi.org/10.1016/j.atmosenv.2020.118088.

Singh N, R K Mall, T Banerjee, A Gupta, 2021b, "Associations between climate, and infectious diseases among children in Varanasi City, India: A Prospective Cohort Study", *Sci. Total Environ.* **796**, 148769. https://doi.org/10.1016/j.scitotenv.2021.148769.

Singh N, Mhawish A, Ghosh S, Banerjee T and Mall R K, 2019, "Attributing mortality from temperature extremes: A time series analysis in Varanasi, India", *Sci. Total Environ.* **665** 453–464, https://doi.org/10.1016/j.scitotenv.2019.02.074.

USEPA, 2024, "Research on Health Effects from Air Pollution", https://www.epa.gov/air-research/research-health-effects-air-pollution.

Van Hee V C, Adar S D, Szpiro A A, Barr R G, Bluemke D A, Diez Roux A V, Gill E A, Sheppard L and Kaufman J D, 2009, "Exposure to Traffic and Left Ventricular Mass and Function", *Am. J. Respir. Crit. Care Med.* **179** 827–834, https://doi.org/10.1164/rccm.200808-1344OC.

VanderWeele T J and Ding P, 2017, "Sensitivity Analysis in Observational Research: Introducing the E-Value", *Ann. Intern. Med.* **167** 268–274, https://doi.org/10.7326/M16-2607.

von Elm E, Altman D G, Egger M, Pocock S J, Gøtzsche P C and Vandenbroucke J P for the STROBE Initiative, 2007, "The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies*", *Bull. World Health Organ.* **85** 867–872, https://doi.org/10.2471/BLT.07.045120.

Wellenius G A, Yeh G Y, Coull B A, Suh H H, Phillips R S and Mittleman M A, 2007, "Effects of ambient air pollution on functional status in patients with chronic congestive heart failure: a repeated-measures study", *Environ. Health* **6** 26, https://doi.org/10.1186/1476-069X-6-26.

WHO 2021, "What are the WHO Air quality guidelines? Improving health by reducing air pollution", https://www.who.int/news-room/feature-stories/detail/what-are-the-who-air-quality-guidelines.

WHO 2014, "7-million-premature-deaths-annually-linked-to-air-pollution", https://www.who.int/news/item/25-03-2014-7-million-premature-deaths-annually-linked-to-air-pollution.

Wood S N, 2006, "Generalized Additive Models: an Introduction with R", Chapman and Hall/CRC. Chapman and Hall/CRC.

Xi Y, Kshirsagar A V, Wade T J, Richardson D B, Brookhart M A, Wyatt L and Rappold A G, 2020, "Mortality in US Hemodialysis Patients Following Exposure to Wildfire Smoke", *J. Am. Soc. Nephrol.* **31** 1824, https://doi.org/10.1681/ASN.2019101066.

Zeka A, Sullivan J R, Vokonas P S, Sparrow D and Schwartz J, 2006, "Inflammatory markers and particulate air pollution: characterizing the pathway to disease", *Int. J. Epidemiol.* **35** 1347–1354, https://doi.org/10.1093/ije/dyl132.

Zheng S, Schlink U, Ho K -F, Singh R P and Pozzer A, 2021, "Spatial Distribution of PM2.5-Related Premature Mortality in China", *GeoHealth* **5** e2021GH000532, https://doi.org/10.1029/2021GH000532.

Supplementary Figures

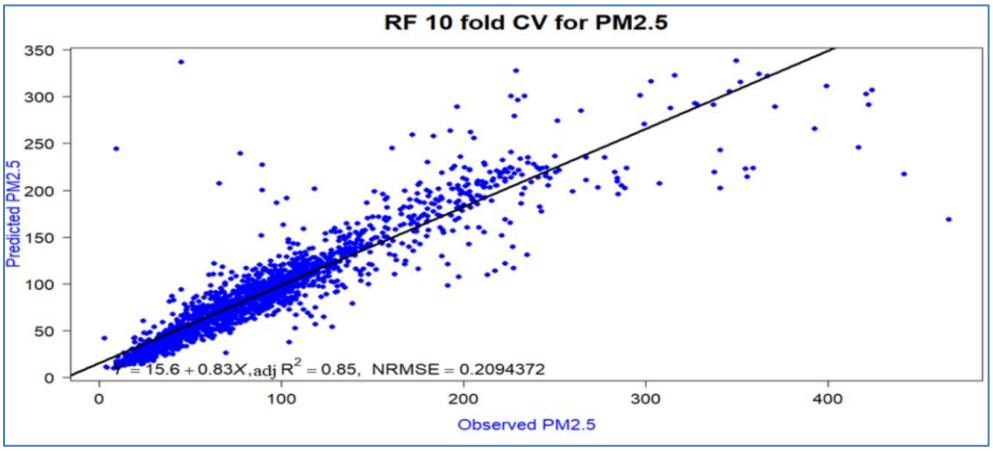

Fig. S1. Scatter plot shows results from a 10-fold cross-validation between observed and predicted values for $PM_{2.5}$ using the random forest machine-learning algorithm

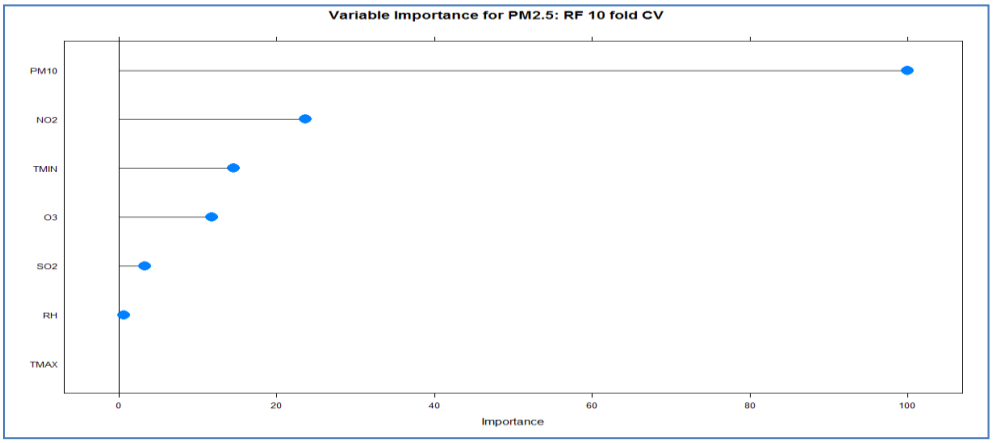

Fig. S2. Variable importance plot while performing a 10-fold cross-validation for $PM_{2.5}$ using the random forest machine-learning algorithm

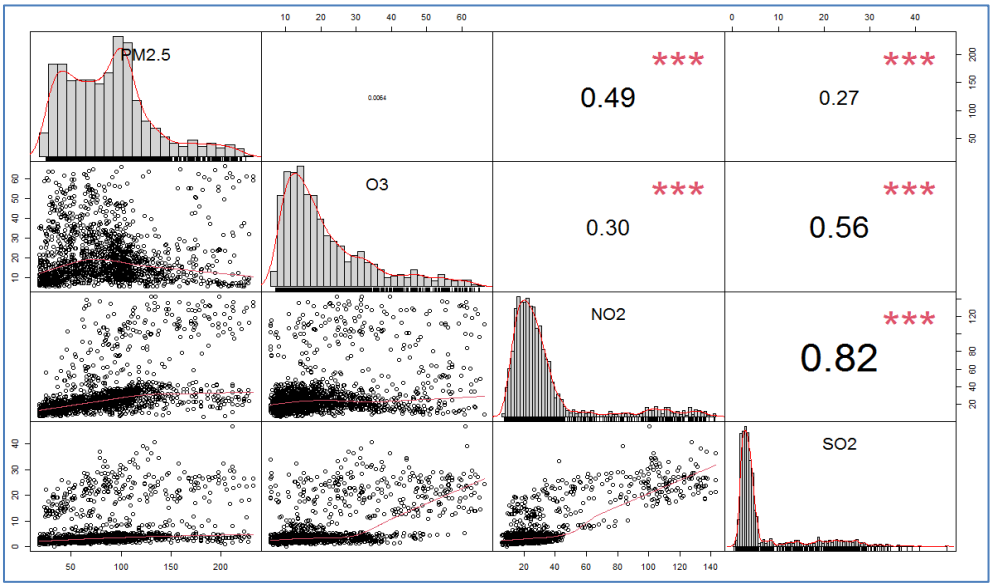

Fig. S3. Correlation analyses among the air pollution variables

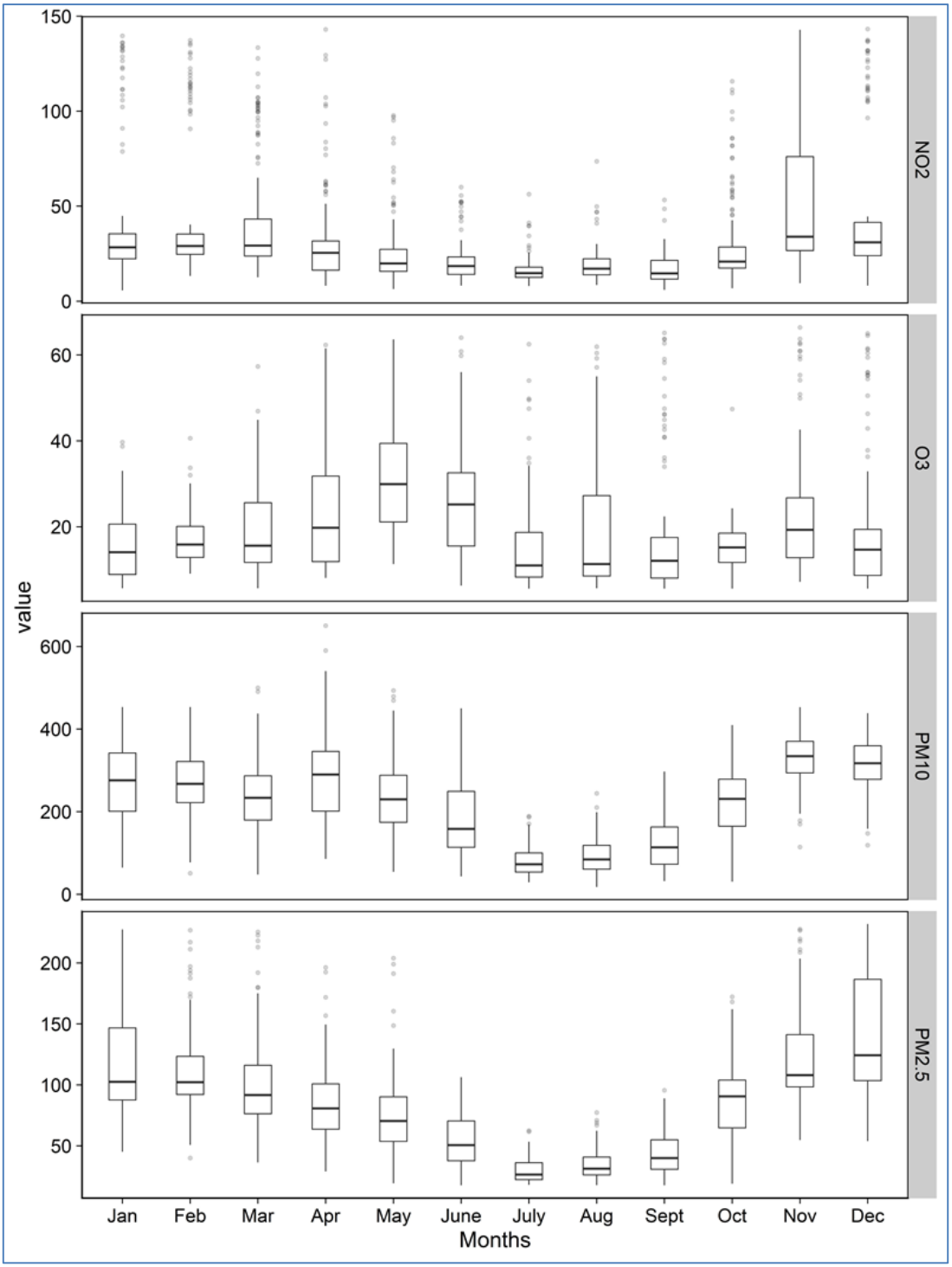

Fig. S4. Monthly variability of air pollutants ($PM_{2.5}$, O_3, and NO_2). Also shown is the variability of PM_{10} just because $PM_{2.5}$ was imputed using PM_{10} along with other variables

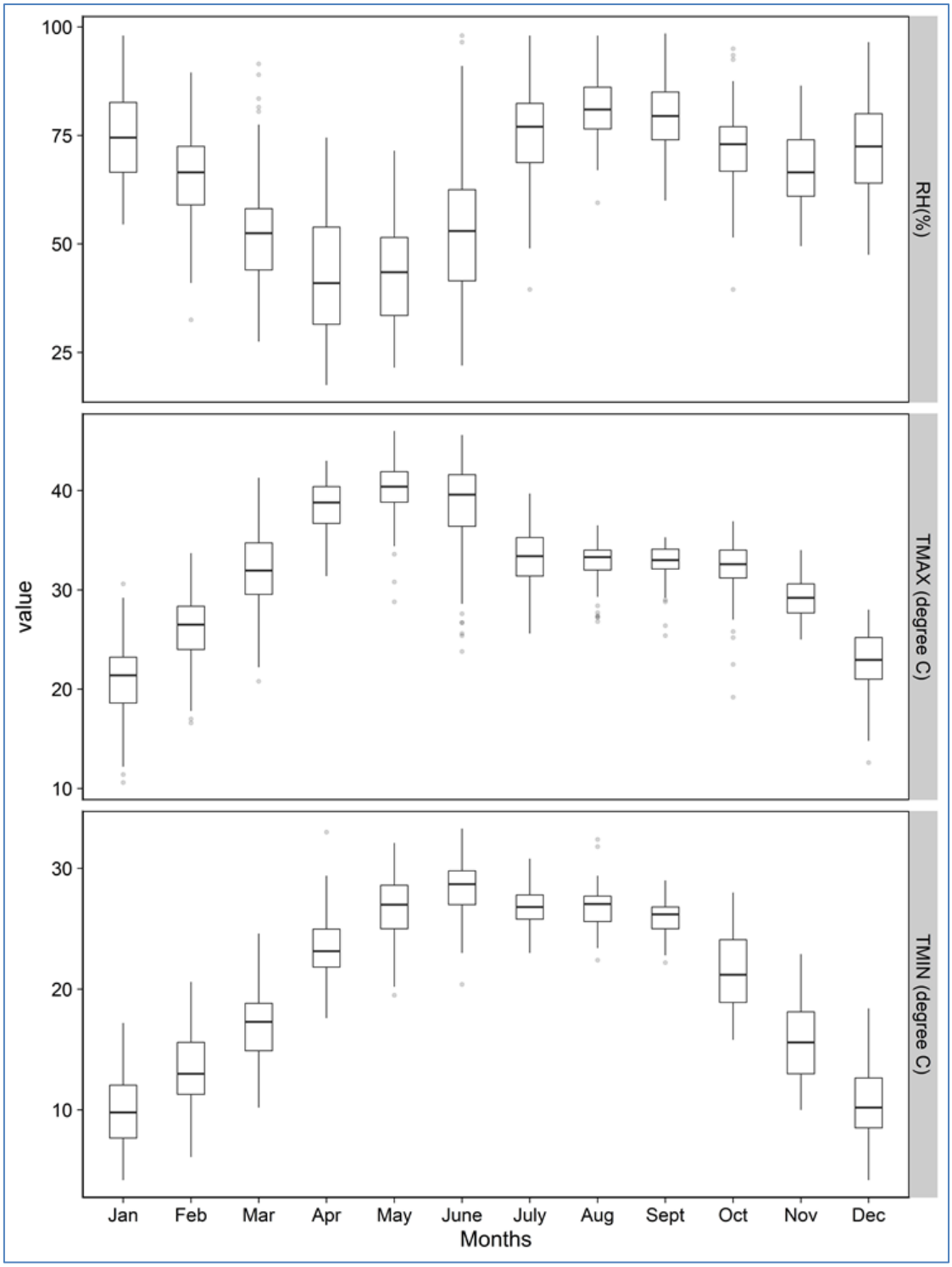

Fig. S5. Monthly variability of meteorological parameters

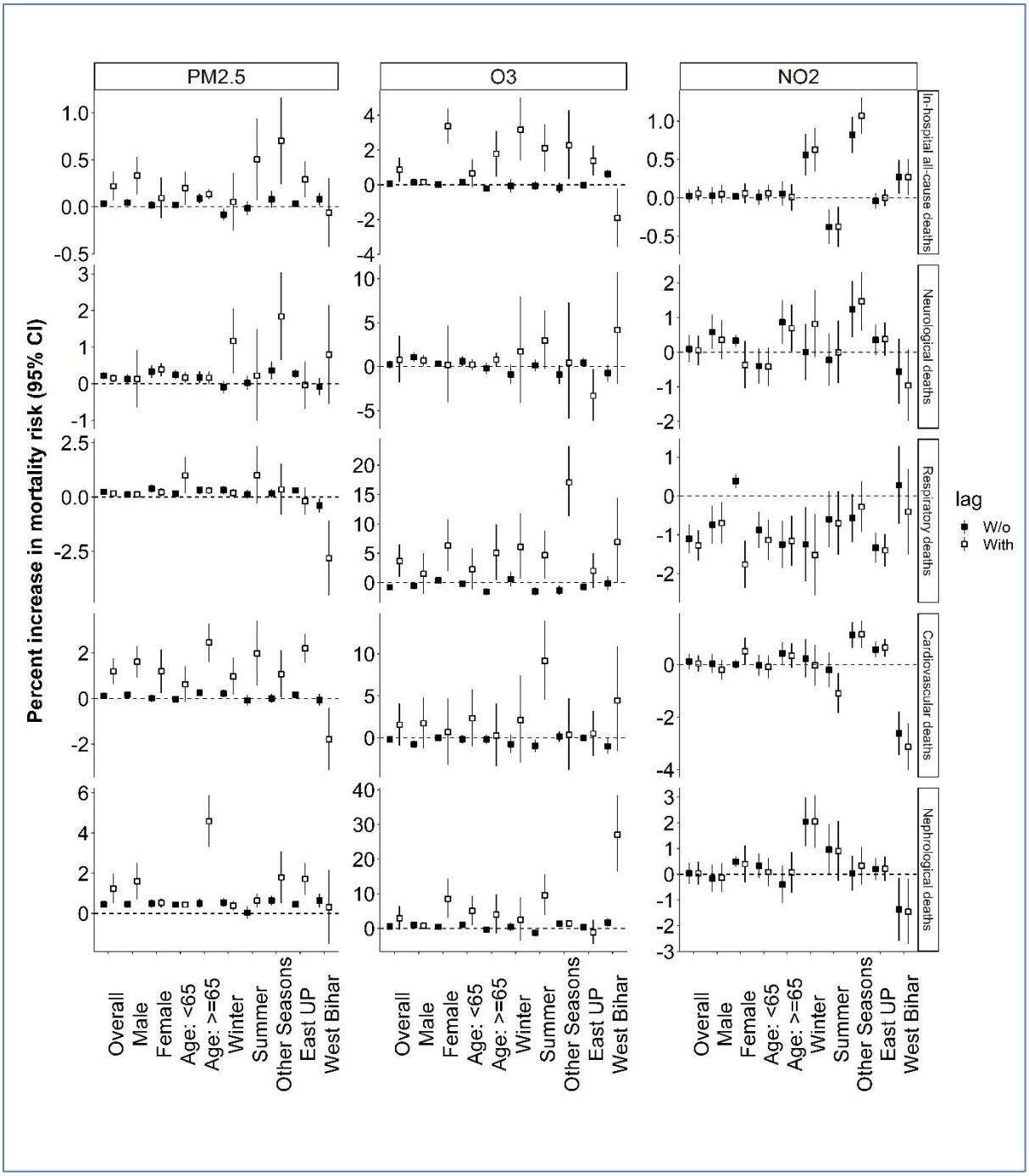

Fig. S6. Percent increase (and 95% CI) in daily adjusted mortality risks associated with a 1 unit increase in $PM_{2.5}$, O_3, and NO_2 by sex, age, season, and region for with and without lag effect scenarios

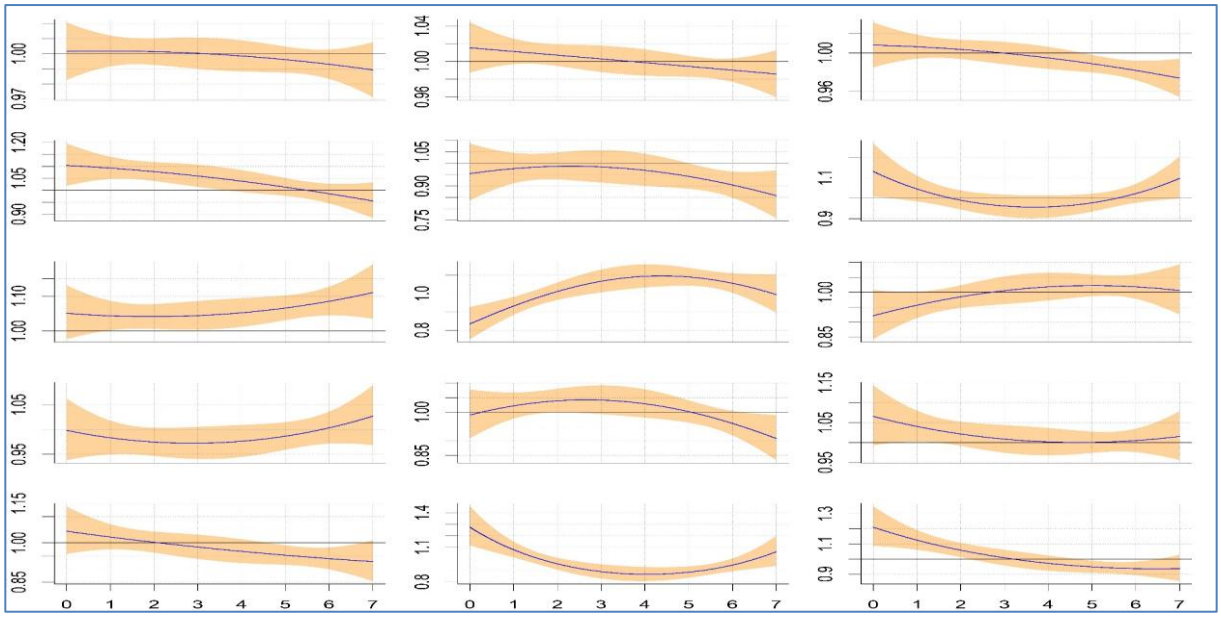

Fig. S7. Mortality risks (and 95% CI) per IQR increase in air pollutants ($PM_{2.5}$, O_3, and NO_2) at different lags from the distributed lag model for in-hospital all-cause deaths; neurological deaths; respiratory deaths; cardiovascular deaths; and nephrological deaths for Varanasi only

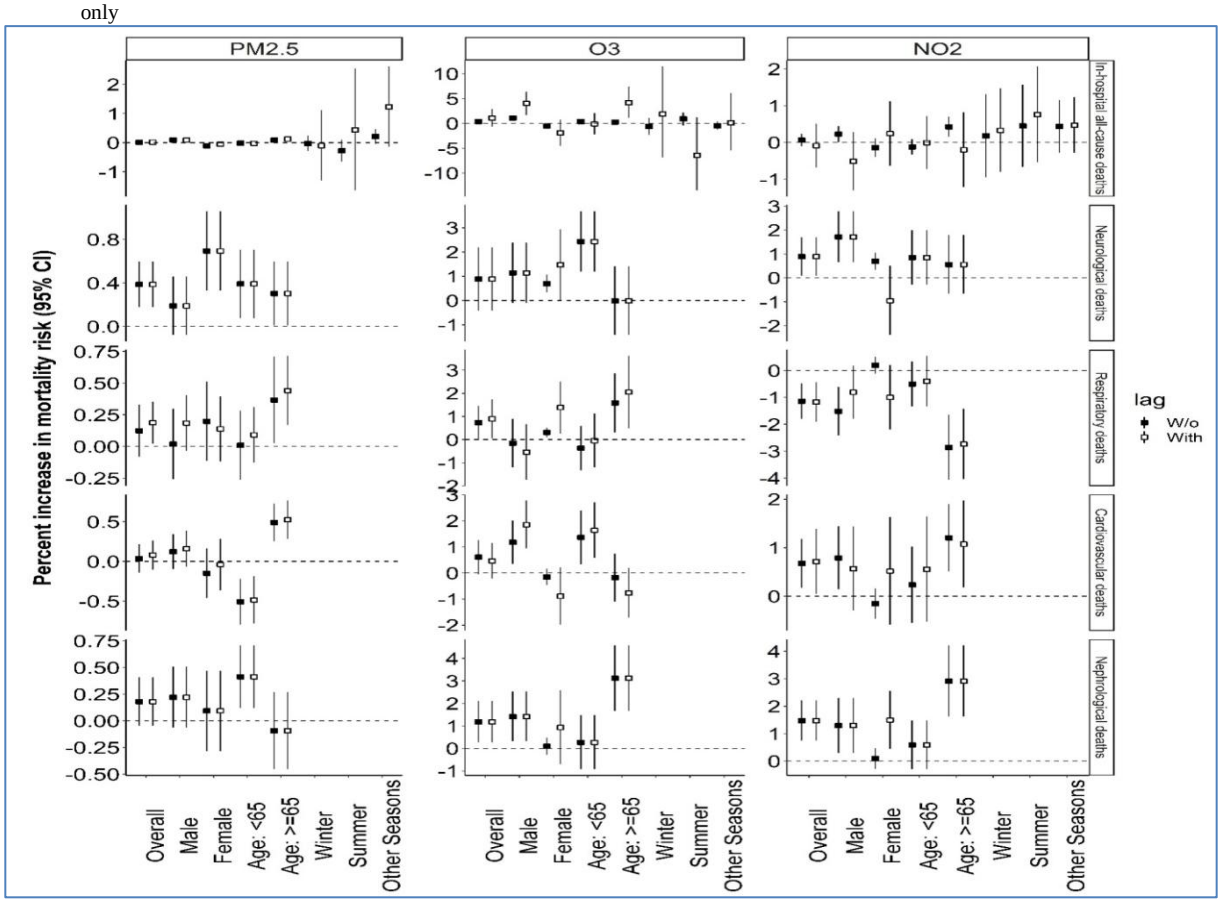

Fig. S8. Percent increase (and 95% CI) in daily adjusted mortality risks associated with a 1 unit increase in $PM_{2.5}$, O_3, and NO_2 by sex, age, season, and region for with and without lag effect scenarios for Varanasi only. Segregated data by season were not enough to get estimates from modeling (and so not shown here), exception being that for the in-hospital all-cause deaths

TABLE S1

District-wise and total population details of actual study area (source: Census, 2011)

Sr. No.	Districts	Lat (N)	Long (East)	Pop-2011	Male-all-age-2011	Female-all-age-2011	Area (sq. km)	Density (per sq. km)
1	Arrah	25.5541	84.6665	4,62,618	2,45,242	2,17,376	191.20	2,420
2	Prayagraj/ Allahabad	25.4358	81.8463	59,54,391	31,31,807	28,22,584	5482.00	1,086
3	Ambedkarnagar/ Amethi/Faizabad	26.4684	82.6915	23,97,888	12,12,410	11,85,478	2350.00	1,020
4	Azamgarh	26.0739	83.1859	46,13,913	22,85,004	23,28,909	4054.00	1,138
5	Vaishali	25.6838	85.355	34,95,021	18,44,535	16,50,486	2036.00	1,717
6	Ballia	25.8307	84.1857	32,39,774	16,72,902	15,66,872	2981.00	1,087
7	Balrampur	27.4307	82.1805	21,48,665	11,14,721	10,33,944	3349.00	642
8	Basti	26.814	82.763	24,64,464	12,55,272	12,09,192	2688.00	917
9	Bhabhua/Mohania/Kaimur	25.0426	83.6056	16,26,384	8,47,006	7,79,378	3332.00	488
10	Bhadohi	25.3805	82.5677	15,78,213	8,07,099	7,71,114	1015.00	1,555
11	Bhojpur	25.4662	84.5222	27,28,407	14,30,380	12,98,027	2395.00	1,139
12	Buxar	25.5647	83.9777	17,06,352	8,87,977	8,18,375	1703.00	1,002
13	Bettiah/ West Champaran	27.1543	84.3542	2,24,200	1,17,771	1,06,429	68.13	3,291
14	Chandauli	25.2605	83.2645	19,52,756	10,17,905	9,34,851	2541.00	768
15	Chhapara/Saran	25.7811	84.7543	1,23,024	62,321	60,703	901.39	136
16	Darbhanga	26.1542	85.8918	39,37,385	20,59,949	18,77,436	2279.00	1,728
17	Deoria	26.5024	83.7791	31,00,946	15,37,436	15,63,510	2540.00	1,221
18	Dinara/Sasaram/Rohtas	25.2448	84.067	29,59,918	15,43,546	14,16,372	3881.00	763
19	Motihari/ East Champaran	26.6098	84.8568	3,63,976	1,94,253	1,69,723	236.97	1,536
20	Gaya	24.7914	85.0002	43,91,418	22,66,566	21,24,852	4976.00	883
21	Ghazipur	25.5878	83.5783	36,20,268	18,55,075	17,65,193	3377.00	1,072
22	Ghosi/Mau	26.1157	83.5443	4,67,413	2,32,720	2,34,693	347.48	1,345
23	Gonda	27.134	81.9619	34,33,919	17,87,146	16,46,773	4003.00	858
24	Gopalganj	26.4832	84.4366	25,62,012	12,67,666	12,94,346	2033.00	1,260
25	Gorakhpur	26.7606	83.3732	44,40,895	22,77,777	21,63,118	3321.00	1,337
26	Shahganj/ Jaunpur	25.7464	82.6837	44,94,204	22,20,465	22,73,739	4038.00	1,113
27	Kushinagar	26.7399	83.887	35,64,544	18,18,055	17,46,489	2905.00	1,227
28	Maharajganj	27.1446	83.5622	4,33,664	2,24,565	2,09,099	722.76	600
29	Mirzapur	25.1337	82.5644	24,96,970	13,12,302	11,84,668	4405.00	567
30	Muzaffarpur	26.1197	85.391	48,01,062	25,27,497	22,73,565	3172.00	1,514
31	Nalanda	25.2622	85.4788	28,77,653	14,97,060	13,80,593	2355.00	1,222
32	Patna	25.5941	85.1376	58,38,465	30,78,512	27,59,953	3202.00	1,823
33	Pratapgarh	25.915	81.9801	8,67,848	4,37,744	4,30,104	4449.00	195
34	Rae Bareli	26.2145	81.2528	34,05,559	17,52,542	16,53,017	4609.00	739
35	Samastipur	25.856	85.7868	42,61,566	22,30,003	20,31,563	2904.00	1,467
36	Siwan	26.2243	84.36	33,30,464	16,75,090	16,55,374	2219.00	1,501
37	Sonbhadra	24.685	83.0684	18,62,559	9,71,344	8,91,215	6905.00	270
38	Sultanpur	26.2585	82.066	37,97,117	19,14,586	18,82,531	4436.00	856
39	Varanasi	25.3176	82.9739	36,76,841	19,21,857	17,54,984	1535.00	2,395
40	TOTAL			10,97,02,736	5,65,36,108	5,31,66,628	1,09,938	998

TABLE S2

Sensitivity analysis for marginal estimates (reported in table 3) assuming ±30% uncertainty in each of the $PM_{2.5}$, O_3, or NO_2 exposures assessment. These results, based on inverse probability weighting (IPW) causal modeling, show percent increase in adjusted mortality risk (and 95% CI) for specific causes of deaths for a 10 μg m^{-3} change in $PM_{2.5}$, O_3, or NO_2 exposure

Cause of Death	$PM_{2.5}$		O_3		NO_2	
	RR		RR		RR	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
In-hospital all-cause deaths						
Overall	**2.12**	**(1.89, 2.35)**	**1.11**	**(0.97, 1.24)**	-2.27	(-2.48, -2.06)
Male	**0.63**	**(0.46, 0.81)**	**0.53**	**(0.43, 0.63)**	-1.32	(-1.48, -1.16)
Female	**1.48**	**(1.32, 1.64)**	**0.57**	**(0.48, 0.66)**	-0.95	(-1.08, -0.82)
Age: <65	**1.31**	**(1.12, 1.51)**	**0.92**	**(0.80, 1.04)**	-2.40	(-2.58, -2.22)
Age: >=65	**0.80**	**(0.69, 0.90)**	**0.18**	**(0.12, 0.25)**	**0.13**	**(0.03, 0.23)**
Winter	**6.75**	**(6.38, 7.11)**	**1.32**	**(1.13, 1.51)**	**1.08**	**(0.75, 1.42)**
Summer	-0.58	(-0.89, -0.26)	**0.66**	**(0.48, 0.84)**	**2.65**	**(2.48, 2.83)**
Other Seasons	-4.05	(-4.39, -3.71)	-0.87	(-1.08, -0.66)	-6.02	(-6.34, -5.69)
East UP	**1.34**	**(1.10, 1.58)**	**1.84**	**(1.70, 1.98)**	-1.47	(-1.67, -1.27)
West Bihar	**0.77**	**(0.63, 0.91)**	-0.73	(-0.79, -0.66)	-0.80	(-0.88, -0.71)
Neurological deaths						
Overall	**0.07**	**(0.02, 0.12)**	**0.17**	**(0.12, 0.22)**	-0.08	(-0.11, -0.05)
Male	0.03	(-0.01, 0.07)	**0.05**	**(0.01, 0.09)**	**0.03**	**(0.01, 0.05)**
Female	**0.04**	**(0.01, 0.07)**	**0.13**	**(0.10, 0.16)**	-0.10	(-0.13, -0.08)
Age: <65	-0.20	(-0.24, -0.16)	**0.17**	**(0.13, 0.21)**	-0.11	(-0.13, -0.09)
Age: >=65	**0.27**	**(0.24, 0.30)**	0.02	(-0.01, 0.05)	**0.03**	**(0.01, 0.05)**
Winter	**0.13**	**(0.09, 0.16)**	-0.06	(-0.09, -0.03)	**0.10**	**(0.08, 0.12)**
Summer	**0.04**	**(0.01, 0.07)**	**0.22**	**(0.19, 0.26)**	**0.06**	**(0.04, 0.08)**
Other Seasons	-0.09	(-0.12, -0.06)	0.01	(-0.02, 0.04)	-0.24	(-0.26, -0.21)
East UP	-0.03	(-0.07, 0.02)	**0.15**	**(0.11, 0.19)**	-0.05	(-0.08, -0.02)
West Bihar	**0.10**	**(0.07, 0.12)**	**0.04**	**(0.02, 0.06)**	-0.03	(-0.04, -0.01)
Respiratory deaths						
Overall	**0.54**	**(0.49, 0.59)**	**0.27**	**(0.24, 0.30)**	-0.17	(-0.23, -0.11)
Male	**0.61**	**(0.57, 0.66)**	**0.25**	**(0.22, 0.28)**	-0.13	(-0.18, -0.08)
Female	**0.07**	**(0.04, 0.10)**	0.02	(-0.01, 0.04)	-0.06	(-0.09, -0.02)
Age: <65	**0.28**	**(0.24, 0.32)**	**0.12**	**(0.09, 0.15)**	-0.25	(-0.30, -0.20)
Age: >=65	**0.26**	**(0.24, 0.28)**	**0.11**	**(0.09, 0.13)**	**0.06**	**(0.03, 0.10)**
Winter	**0.40**	**(0.35, 0.45)**	**0.10**	**(0.08, 0.12)**	**0.29**	**(0.26, 0.33)**
Summer	**0.05**	**(0.04, 0.06)**	**0.04**	**(0.02, 0.06)**	**0.09**	**(0.05, 0.14)**
Other Seasons	**0.09**	**(0.06, 0.11)**	**0.20**	**(0.18, 0.23)**	-0.38	(-0.41, -0.34)
East UP	**0.19**	**(0.15, 0.23)**	**0.13**	**(0.10, 0.16)**	-0.21	(-0.26, -0.16)
West Bihar	**0.35**	**(0.33, 0.37)**	**0.10**	**(0.08, 0.12)**	0.02	(-0.01, 0.0.05)
Cardiovascular deaths						
Overall	**0.17**	**(0.11, 0.23)**	**0.13**	**(0.08, 0.18)**	**0.20**	**(0.14, 0.26)**
Male	**0.11**	**(0.06, 0.15)**	**0.35**	**(0.30, 0.39)**	-0.27	(-0.32, -0.22)
Female	**0.06**	**(0.03, 0.09)**	-0.21	(-0.24, -0.18)	**0.48**	**(0.44, 0.52)**
Age: <65	-0.02	(-0.06, 0.02)	-0.04	(-0.08, -0.01)	**0.26**	**(0.21, 0.31)**
Age: >=65	**0.16**	**(0.12, 0.19)**	**0.18**	**(0.15, 0.21)**	-0.06	(-0.09, -0.02)
Winter	**0.55**	**(0.51, 0.59)**	0.02	(-0.02, 0.07)	-0.19	(-0.23, -0.15)

Cause of Death	$PM_{2.5}$		O_3		NO_2	
	RR		RR		RR	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Summer	**0.32**	**(0.28, 0.36)**	-0.003	(-0.012, 0.006)	-0.02	(-0.05, 0.01)
Other Seasons	**0.41**	**(0.36, 0.45)**	**0.11**	**(0.07, 0.15)**	**0.41**	**(0.36, 0.46)**
East UP	**0.06**	**(0.01, 0.11)**	**0.39**	**(0.34, 0.44)**	**0.16**	**(0.11, 0.21)**
West Bihar	**0.23**	**(0.20, 0.26)**	-0.26	(-0.28, -0.24)	**0.05**	**(0.02, 0.07)**
Nephrological deaths						
Overall	**0.03**	**(0.01, 0.05)**	**0.09**	**(0.04, 0.14)**	-0.19	(-0.22, -0.16)
Male	**0.30**	**(0.25, 0.35)**	0.01	(-0.03, 0.04)	0.01	(-0.02, 0.03)
Female	-0.27	(-0.30, -0.23)	**0.08**	**(0.05, 0.11)**	-0.19	(-0.21, -0.18)
Age: <65	0.04	(-0.01, 0.09)	**0.08**	**(0.04, 0.13)**	-0.10	(-0.12, -0.08)
Age: >=65	-0.01	(-0.03, 0.02)	0.01	(-0.02, 0.03)	-0.09	(-0.10, -0.07)
Winter	**0.68**	**(0.64, 0.72)**	-0.02	(-0.05, 0.01)	**0.09**	**(0.07, 0.11)**
Summer	-0.16	(-0.19, -0.12)	**0.12**	**(0.10, 0.15)**	**0.03**	**(0.02, 0.04)**
Other Seasons	-0.49	(-0.53, -0.45)	-0.01	(-0.05, 0.03)	-0.31	(-0.33, -0.28)
East UP	-0.19	(-0.24, -0.14)	**0.09**	**(0.04, 0.14)**	-0.17	(-0.19, -0.14)
West Bihar	**0.22**	**(0.19, 0.25)**	-0.01	(-0.03, 0.01)	-0.02	(-0.03, -0.01)

TABLE S3

Percent increase in adjusted mortality risk (and 95% CI) for specific causes of death for a 10 μg m^{-3} change in $PM_{2.5}$, O_3, or NO_2 exposure

Cause of Death	$PM_{2.5}$		O_3		NO_2	
	% change in mortality		% change in mortality		% change in mortality	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
In-hospital all-cause deaths						
Overall	**2.19**	**(0.64, 3.74)**	**8.69**	**(1.65, 15.78)**	0.55	(-0.38, 1.47)
Male	**3.33**	**(1.33, 5.33)**	**1.67**	**(0.11, 3.24)**	0.48	(-0.73, 1.69)
Female	0.93	(-1.23, 3.10)	**33.77**	**(23.64, 43.99)**	0.58	(-0.69, 1.86)
Age: <65	**2.00**	**(0.22, 3.80)**	6.55	(-1.46, 14.62)	0.60	(-0.46, 1.66)
Age: >=65	**1.33**	**(0.80, 1.87)**	**17.83**	**(4.60, 31.24)**	0.06	(-1.65, 1.78)
Winter	0.54	(-2.50, 3.59)	**31.80**	**(13.81, 50.11)**	**6.29**	**(3.44, 9.13)**
Summer	**5.04**	**(0.71, 9.40)**	**21.15**	**(7.47, 35.02)**	-3.80	(-6.42, -1.17)
Other Seasons	**7.02**	**(2.45, 11.62)**	**22.89**	**(3.34, 42.83)**	**10.69**	**(8.32, 13.06)**
East UP	**2.92**	**(1.02, 4.83)**	**13.83**	**(5.25, 22.49)**	0.01	(-1.10, 1.12)
West Bihar	-0.63	(-4.27, 3.03)	-19.09	(-35.77, -2.13)	**2.69**	**(0.31, 5.07)**
Neurological deaths						
Overall	**1.54**	**(0.41, 2.68)**	7.94	(-18.26, 34.84)	0.50	(-3.79, 4.80)
Male	1.33	(-6.47, 9.19)	**6.98**	**(0.54, 13.47)**	3.56	(-2.03, 9.17)
Female	**3.86**	**(2.04, 5.69)**	2.01	(-40.71, 46.63)	-3.66	(-10.50, 3.23)
Age: <65	**1.66**	**(0.21, 3.12)**	2.25	(-4.06, 8.59)	-4.19	(-9.73, 1.39)
Age: >=65	1.61	(-0.16, 3.38)	**8.06**	**(0.08, 16.11)**	**6.92**	**(0.19, 13.70)**
Winter	**11.70**	**(2.88, 20.59)**	17.34	(-41.47, 79.76)	8.19	(-1.52, 18.00)
Summer	2.22	(-10.25, 14.85)	29.61	(-3.06, 63.34)	0.02	(-9.01, 9.13)
Other Seasons	**18.39**	**(6.39, 30.53)**	4.48	(-59.33, 72.61)	**14.71**	**(6.31, 23.18)**
East UP	-0.37	(-6.84, 6.14)	-33.06	(-62.11, -3.11)	3.78	(-1.00, 8.58)
West Bihar	7.93	(-5.47, 21.51)	41.84	(-19.97, 107.54)	-9.57	(-19.96, 0.93)

Cause of Death	$PM_{2.5}$		O_3		NO_2	
	% change in mortality		% change in mortality		% change in mortality	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Respiratory deaths						
Overall	**1.77**	**(0.63, 2.92)**	**37.23**	**(9.88, 65.33)**	-12.72	(-16.63, -8.79)
Male	1.34	(-0.11, 2.80)	14.97	(-19.28, 50.42)	-6.93	(-12.27, -1.55)
Female	**2.30**	**(0.34, 4.26)**	**63.10**	**(19.88, 108.14)**	-17.59	(-23.66, -11.48)
Age: <65	**9.97**	**(1.65, 18.35)**	22.73	(-11.60, 58.25)	-11.30	(-16.43, -6.14)
Age: >=65	**3.08**	**(1.27, 4.90)**	**50.78**	**(4.17, 99.56)**	-11.56	(-17.97, -5.11)
Winter	1.95	(-0.02, 3.93)	**60.72**	**(6.53, 117.83)**	-15.18	(-25.62, -4.62)
Summer	10.03	(-3.11, 23.35)	**46.68**	**(6.59, 88.37)**	-6.99	(-15.14, 1.23)
Other Seasons	3.46	(-8.21, 15.27)	**170.99**	**(112.87, 232.15)**	-2.75	(-9.28, 3.83)
East UP	-1.83	(-8.12, 4.49)	19.94	(-8.99, 49.72)	-13.98	(-18.15, -9.79)
West Bihar	-28.13	(-45.26, -10.69)	69.33	(-0.63, 144.20)	-4.05	(-15.04, 7.06)
Cardiovascular deaths						
Overall	**11.89**	**(6.29, 17.52)**	15.61	(-9.07, 40.91)	0.48	(-2.67, 3.63)
Male	**16.14**	**(9.32, 23.00)**	17.28	(-13.02, 48.52)	-1.99	(-5.85, 1.89)
Female	**11.91**	**(2.44, 21.48)**	6.92	(-32.04, 47.43)	5.15	(-0.02, 10.35)
Age: <65	6.25	(-1.41, 13.96)	23.37	(-9.81, 57.65)	-0.86	(-5.12, 3.43)
Age: >=65	**24.53**	**(16.12, 33.01)**	2.60	(-34.17, 40.77)	3.46	(-1.26, 8.20)
Winter	**9.69**	**(1.63, 17.83)**	21.25	(-29.61, 74.77)	-0.26	(-7.90, 7.44)
Summer	**19.80**	**(5.67, 34.13)**	**91.68**	**(45.67, 139.70)**	-10.92	(-18.54, -3.23)
Other Seasons	**10.67**	**(0.36, 21.09)**	3.64	(-38.10, 47.20)	**11.58**	**(6.40, 16.79)**
East UP	**21.97**	**(15.75, 28.22)**	5.02	(-21.72, 32.49)	**6.49**	**(3.13, 9.86)**
West Bihar	-17.77	(-31.26, -4.10)	44.59	(-15.81, 108.71)	-31.32	(-40.08, -22.48)
Nephrological deaths						
Overall	**12.37**	**(5.10, 19.70)**	29.63	(-3.76, 64.15)	0.31	(-4.14, 4.78)
Male	**16.04**	**(7.00, 25.15)**	**7.79**	**(0.79, 14.84)**	-1.38	(-7.05, 4.31)
Female	**5.26**	**(3.07, 7.45)**	**85.40**	**(29.80, 144.00)**	4.00	(-3.06, 11.12)
Age: <65	**4.38**	**(2.75, 6.02)**	**50.77**	**(9.66, 93.56)**	0.84	(-4.52, 6.24)
Age: >=65	**45.94**	**(33.10, 58.93)**	40.73	(-13.60, 98.05)	0.64	(-7.20, 8.55)
Winter	**3.90**	**(1.58, 6.23)**	24.88	(-36.88, 90.59)	**20.50**	**(10.27, 30.83)**
Summer	**6.40**	**(2.77, 10.03)**	**95.61**	**(37.99, 156.43)**	8.96	(-2.61, 20.67)
Other Seasons	**17.98**	**(5.12, 31.01)**	**14.11**	**(5.13, 23.18)**	3.34	(-3.96, 10.69)
East UP	**17.23**	**(9.33, 25.20)**	-11.03	(-45.48, 24.67)	2.11	(-2.60, 6.84)
West Bihar	3.05	(-15.25, 21.68)	**270.73**	**(165.51, 385.45)**	-14.58	(-27.16, -1.84)

TABLE S4

Characteristics of pooled mortality and cause-specific mortality for Varanasi only, 2012–2018

Category	Total deaths (% of total)	Mean daily deaths (SD)
In-hospital all-cause deaths	6174 (100)	2.41 (1.67)
Sex		
Female	2629 (42.6)	1.03 (1.05)
Male	3545 (57.4)	1.38 (1.22)
Age group		
< 65 Y	4343 (70.3)	1.70 (1.38)
≥ 65 Y	1831 (29.7)	0.72 (0.87)
Season		
Winter	1106 (17.9)	0.43 (1.17)

Category	Total deaths (% of total)	Mean daily deaths (SD)
Summer	1050 (17.0)	0.41 (1.15)
Other Seasons	4018 (65.1)	1.57 (1.75)
Neurological deaths	372 (100)	0.15 (0.38)
Sex		
Female	146 (39.2)	0.06 (0.24)
Male	226 (60.8)	0.09 (0.30)
Age group		
< 65 Y	218 (58.6)	0.09 (0.29)
≥ 65 Y	154 (41.4)	0.06 (0.24)
Season		
Winter	87 (23.4)	0.03 (0.20)
Summer	72 (19.4)	0.03 (0.17)
Other Seasons	213 (57.2)	0.08 (0.30)
Respiratory deaths	413 (100)	0.16 (0.39)
Sex		
Female	179 (43.3)	0.07 (0.26)
Male	234 (56.7)	0.09 (0.30)
Age group		
< 65 Y	268 (64.9)	0.10 (0.32)
≥ 65 Y	145 (35.1)	0.06 (0.24)
Season		
Winter	59 (14.3)	0.02 (0.15)
Summer	92 (22.3)	0.04 (0.21)
Other Seasons	262 (63.4)	0.10 (0.32)
Cardiovascular deaths	481 (100)	0.18 (0.43)
Sex		
Female	188 (39.1)	0.07 (0.27)
Male	293 (60.9)	0.11 (0.34)
Age group		
< 65 Y	257 (53.4)	0.10 (0.31)
≥ 65 Y	224 (46.6)	0.09 (0.29)
Season		
Winter	79 (16.4)	0.03 (0.19)
Summer	75 (15.6)	0.03 (0.19)
Other Seasons	327 (68.0)	0.13 (0.36)
Nephrological deaths	307 (100)	0.12 (0.35)
Sex		
Female	114 (37.1)	0.04 (0.22)
Male	193 (62.9)	0.08 (0.27)
Age group		
< 65 Y	198 (64.5)	0.08 (0.28)
≥ 65 Y	109 (35.5)	0.04 (0.21)
Season		
Winter	71 (23.1)	0.03 (0.18)
Summer	45 (14.7)	0.02 (0.13)
Other Seasons	191 (62.2)	0.07 (0.28)

TABLE S5

Distributed lag effect estimation of air pollutants for pooled mortality risk and cause-specific mortality risks

Distributed lag effect of	Maximum RR observed at lag	Significant RR up to lag
In-hospital all-cause deaths		
$PM_{2.5}$	3	4
O_3	3	5
NO_2	NA	NA
Neurological deaths		
$PM_{2.5}$	2	3
O_3	NA	NA
NO_2	0	2
Respiratory deaths		
$PM_{2.5}$	0	1
O_3	3	5
NO_2	NA	NA
Cardiovascular deaths		
$PM_{2.5}$	0	1
O_3	2	3
NO_2	4	6
Nephrological deaths		
$PM_{2.5}$	0	2
O_3	0	1
NO_2	0	2

RR was calculated per IQR increase in air pollutants. IQR for cause-specific and in-hospital all-cause mortality is given in table 2

TABLE S6

Marginal estimates of adjusted mortality risk (RR and 95% CI), based on inverse probability weighting (IPW) method, for specific causes of death for a 10 μg m^{-3} change in $PM_{2.5}$, O_3, or NO_2 exposure <

Cause of Death	$PM_{2.5}$ RR		O_3 RR		NO_2 RR	
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
In-hospital all-cause deaths						
Overall	**1.0176**	**(1.0157, 1.0195)**	**1.0092**	**(1.0081, 1.0103)**	0.9812	(0.9794, 0.9829)
Male	**1.0053**	**(1.0038, 1.0067)**	**1.0045**	**(1.0036, 1.0053)**	0.9890	(0.9877, 0.9904)
Female	**1.0123**	**(1.0110, 1.0136)**	**1.0047**	**(1.0040, 1.0055)**	0.9921	(0.9911, 0.9932)
Age: <65	**1.0109**	**(1.0093, 1.0125)**	**1.0077**	**(1.0067, 1.0086)**	0.9801	(0.9786, 0.9815)
Age: >=65	**1.0067**	**(1.0058, 1.0075)**	**1.0015**	**(1.0010, 1.0021)**	**1.0011**	**(1.0003, 1.0020)**
Winter	**1.0559**	**(1.0529, 1.0589)**	**1.0110**	**(1.0094, 1.0126)**	**1.0090**	**(1.0062, 1.0118)**
Summer	0.9952	(0.9926, 0.9978)	**1.0055**	**(1.0040, 1.0070)**	**1.0220**	**(1.0205, 1.0234)**
Other Seasons	0.9664	(0.9636, 0.9693)	0.9927	(0.9910, 0.9945)	0.9501	(0.9475, 0.9528)
East UP	**1.0112**	**(1.0092, 1.0131)**	**1.0153**	**(1.0141, 1.0164)**	0.9878	(0.9862, 0.9894)
West Bihar	**1.0064**	**(1.0053, 1.0075)**	0.9939	(0.9934, 0.9945)	0.9934	(0.9926, 0.9941)
Neurological deaths						
Overall	**1.0028**	**(1.0007, 1.0050)**	**1.0072**	**(1.0051, 1.0093)**	0.9967	(0.9954, 0.9979)
Male	1.0012	(0.9994, 1.0029)	**1.0021**	**(1.0005, 1.0037)**	**1.0012**	**(1.0002, 1.0021)**

Cause of Death	$PM_{2.5}$ RR		O_3 RR		NO_2 RR	
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
Female	**1.0016**	**(1.0004, 1.0028)**	**1.0056**	**(1.0044, 1.0068)**	0.9955	(0.9946, 0.9964)
Age: <65	0.9916	(0.9900, 0.9931)	**1.0070**	**(1.0055, 1.0086)**	0.9953	(0.9943, 0.9964)
Age: >=65	**1.0052**	**(1.0037, 1.0067)**	1.0007	(0.9995, 1.0019)	**1.0013**	**(1.0007, 1.0020)**
Winter	**1.0052**	**(1.0037, 1.0067)**	0.9975	(0.9962, 0.9988)	**1.0042**	**(1.0035, 1.0049)**
Summer	**1.0015**	**(1.0001, 1.0029)**	**1.0094**	**(1.0082, 1.0107)**	**1.0024**	**(1.0017, 1.0031)**
Other Seasons	0.9961	(0.9949, 0.9973)	1.0003	(0.9988, 1.0017)	0.9901	(0.9891, 0.9911)
East UP	0.9988	(0.9969, 1.0007)	**1.0062**	**(1.0044, 1.0080)**	0.9977	(0.9966, 0.9988)
West Bihar	**1.0040**	**(1.0031, 1.0050)**	**1.0015**	**(1.0006, 1.0024)**	0.9989	(0.9983, 0.9996)
Respiratory deaths						
Overall	**1.0073**	**(1.0047, 1.0098)**	**1.0224**	**(1.0202, 1.0245)**	0.9888	(0.9873, 0.9902)
Male	**1.0054**	**(1.0032, 1.0076)**	**1.0254**	**(1.0235, 1.0273)**	0.9895	(0.9884, 0.9907)
Female	**1.0024**	**(1.0010, 1.0039)**	0.9970	(0.9959, 0.9981)	1.0008	(0.9999, 1.0016)
Age: <65	**1.0106**	**(1.0086, 1.0126)**	**1.0117**	**(1.0099, 1.0135)**	0.9950	(0.9939, 0.9961)
Age: >=65	**1.0028**	**(1.0013, 1.0043)**	**1.0107**	**(1.0098, 1.0116)**	0.9952	(0.9944, 0.9961)
Winter	**1.0124**	**(1.0109, 1.0138)**	**1.0166**	**(1.0146, 1.0186)**	0.9957	(0.9947, 0.9966)
Summer	**1.0041**	**(1.0022, 1.0060)**	**1.0022**	**(1.0017, 1.0026)**	**1.0017**	**(1.0009, 1.0025)**
Other Seasons	**1.0156**	**(1.0139, 1.0172)**	**1.0036**	**(1.0026, 1.0046)**	0.9914	(0.9903, 0.9925)
East UP	**1.0088**	**(1.0066, 1.0110)**	**1.0078**	**(1.0062, 1.0094)**	0.9945	(0.9933, 0.9958)
West Bihar	1.0009	(0.9999, 1.0019)	**1.0146**	**(1.0137, 1.0154)**	0.9957	(0.9952, 0.9963)
Cardiovascular deaths						
Overall	**1.0072**	**(1.0048, 1.0096)**	**1.0055**	**(1.0032, 1.0078)**	**1.0084**	**(1.0058, 1.0110)**
Male	**1.0045**	**(1.0026, 1.0064)**	**1.0143**	**(1.0124, 1.0162)**	0.9886	(0.9866, 0.9906)
Female	**1.0025**	**(1.0011, 1.0040)**	0.9912	(0.9901, 0.9923)	**1.0200**	**(1.0184, 1.0216)**
Age: <65	1.0006	(0.9988, 1.0025)	0.9981	(0.9964, 0.9997)	**1.0109**	**(1.0089, 1.0129)**
Age: >=65	**1.0064**	**(1.0048, 1.0081)**	**1.0074**	**(1.0062, 1.0087)**	0.9977	(0.9961, 0.9994)
Winter	**1.0229**	**(1.0215, 1.0244)**	1.0009	(0.9990, 1.0028)	0.9922	(0.9905, 0.9940)
Summer	**1.0133**	**(1.0118, 1.0148)**	0.9999	(0.9995, 1.0002)	0.9991	(0.9980, 1.0003)
Other Seasons	**1.0168**	**(1.0150, 1.0187)**	**1.0047**	**(1.0030, 1.0065)**	**1.0171**	**(1.0149, 1.0193)**
East UP	**1.0026**	**(1.0004, 1.0047)**	**1.0162**	**(1.0141, 1.0184)**	**1.0067**	**(1.0044, 1.0090)**
West Bihar	**1.0096**	**(1.0085, 1.0108)**	0.9893	(0.9884, 0.9902)	**1.0019**	**(1.0010, 1.0029)**
Nephrological deaths						
Overall	**1.0011**	**(1.0009, 1.0014)**	**1.0038**	**(1.0017, 1.0059)**	0.9922	(0.9909, 0.9934)
Male	**1.0125**	**(1.0104, 1.0145)**	1.0002	(0.9986, 1.0018)	1.0002	(0.9992, 1.0012)
Female	0.9888	(0.9875, 0.9901)	**1.0034**	**(1.0021, 1.0048)**	0.9920	(0.9912, 0.9927)
Age: <65	1.0015	(0.9994, 1.0036)	**1.0035**	**(1.0018, 1.0052)**	0.9958	(0.9949, 0.9968)
Age: >=65	0.9997	(0.9985, 1.0009)	1.0001	(0.9989, 1.0013)	0.9964	(0.9957, 0.9971)
Winter	**1.0282**	**(1.0266, 1.0298)**	0.9990	(0.9978, 1.0003)	**1.0037**	**(1.0031, 1.0044)**
Summer	0.9934	(0.9919, 0.9949)	**1.0052**	**(1.0042, 1.0062)**	**1.0012**	**(1.0006, 1.0018)**
Other Seasons	0.9795	(0.9780, 0.9811)	0.9996	(0.9979, 1.0013)	0.9873	(0.9862, 0.9884)
East UP	0.9922	(0.9901, 0.9943)	**1.0040**	**(1.0020, 1.0059)**	0.9932	(0.9920, 0.9943)
West Bihar	**1.0090**	**(1.0077, 1.0104)**	0.9997	(0.9989, 1.0004)	0.9990	(0.9985, 0.9995)

TABLE S7

Sensitivity analysis using E-value estimates for the causal estimates of RR (shown in table S3)

Cause of Death	$PM_{2.5}$		O_3		NO_2	
	E-value for RR Mean	E-value for 95% CI	E-value for RR Mean	E-value for 95% CI	E-value for RR Mean	E-value for 95% CI
In-hospital all-cause deaths						
Overall	1.15	1.14	1.10	1.09	1.15	1.15
Male	1.08	1.06	1.07	1.06	1.11	1.10
Female	1.12	1.11	1.07	1.06	1.09	1.08
Age: <65	1.11	1.10	1.09	1.08	1.16	1.15
Age: >=65	1.08	1.08	1.04	1.03	1.03	1.01
Winter	1.29	1.28	1.11	1.10	1.10	1.08
Summer	1.07	1.04	1.07	1.06	1.17	1.16
Other Seasons	1.22	1.21	1.09	1.08	1.28	1.27
East UP	1.11	1.10	1.13	1.13	1.12	1.11
West Bihar	1.08	1.07	1.08	1.08	1.08	1.08
Neurological deaths						
Overall	1.05	1.02	1.09	1.07	1.06	1.04
Male	1.03	1.00	1.04	1.02	1.03	1.01
Female	1.04	1.02	1.08	1.07	1.07	1.06
Age: <65	1.10	1.09	1.09	1.07	1.07	1.06
Age: >=65	1.07	1.06	1.02	1.00	1.03	1.02
Winter	1.07	1.06	1.05	1.03	1.06	1.06
Summer	1.04	1.01	1.10	1.09	1.05	1.04
Other Seasons	1.06	1.05	1.01	1.00	1.11	1.10
East UP	1.03	1.00	1.08	1.07	1.05	1.03
West Bihar	1.06	1.05	1.04	1.02	1.03	1.02
Respiratory deaths						
Overall	1.09	1.07	1.17	1.16	1.11	1.10
Male	1.07	1.05	1.18	1.17	1.11	1.10
Female	1.05	1.03	1.05	1.04	1.02	1.00
Age: <65	1.11	1.10	1.12	1.10	1.07	1.06
Age: >=65	1.05	1.03	1.11	1.10	1.07	1.06
Winter	1.12	1.11	1.14	1.13	1.07	1.06
Summer	1.06	1.04	1.04	1.04	1.04	1.03
Other Seasons	1.14	1.13	1.06	1.05	1.10	1.09
East UP	1.10	1.08	1.09	1.08	1.08	1.06
West Bihar	1.03	1.00	1.13	1.13	1.07	1.06
Cardiovascular deaths						
Overall	1.09	1.07	1.07	1.05	1.10	1.08
Male	1.07	1.05	1.13	1.12	1.11	1.10
Female	1.05	1.03	1.10	1.09	1.16	1.15
Age: <65	1.02	1.00	1.04	1.01	1.11	1.10
Age: >=65	1.08	1.07	1.09	1.08	1.05	1.02
Winter	1.17	1.16	1.03	1.00	1.09	1.08
Summer	1.12	1.12	1.01	1.00	1.03	1.00
Other Seasons	1.14	1.13	1.07	1.05	1.14	1.13

Cause of Death	$PM_{2.5}$		O_3		NO_2	
	E-value for RR Mean	E-value for 95% CI	E-value for RR Mean	E-value for 95% CI	E-value for RR Mean	E-value for 95% CI
East UP	1.05	1.02	1.14	1.13	1.08	1.07
West Bihar	1.10	1.10	1.11	1.10	1.04	1.03
Nephrological deaths						
Overall	1.03	1.03	1.06	1.04	1.09	1.08
Male	1.12	1.11	1.01	1.00	1.01	1.00
Female	1.11	1.11	1.06	1.04	1.09	1.09
Age: <65	1.04	1.00	1.06	1.04	1.06	1.05
Age: >=65	1.01	1.00	1.01	1.00	1.06	1.05
Winter	1.19	1.19	1.03	1.00	1.06	1.05
Summer	1.08	1.07	1.07	1.06	1.03	1.02
Other Seasons	1.16	1.15	1.02	1.00	1.12	1.12
East UP	1.09	1.08	1.06	1.04	1.08	1.08
West Bihar	1.10	1.09	1.01	1.00	1.03	1.02

TABLE S8

Shift in distribution of $PM_{2.5}$, O_3, and NO_2 by ±30% done for performing sensitivity analysis

Air pollution	Ambient concentrations	-30%	+30%
	(Mean ± SD)		
$PM_{2.5}$ (μg m^{-3})	84.7 ± 46.2	61.9 ± 34.8	114.9 ± 64.6
O_3 (ppb)	20.6 ± 13.2	14.6 ± 9.2	27.1 ± 17.2
NO_2 (ppb)	31.9 ± 27.7	23.09 ± 20.3	42.9 ± 37.7

TABLE S9

Distributed lag effect estimation of air pollutants for pooled mortality risk and cause-specific mortality risks for Varanasi only

Distributed lag effect of	Maximum RR at lag	Significant RR up to lag
In-hospital all-cause deaths		
$PM_{2.5}$	NA	NA
O_3	NA	NA
NO_2	NA	NA
Neurological deaths		
$PM_{2.5}$	0	3
O_3	NA	NA
NO_2	0	0
Respiratory deaths		
$PM_{2.5}$	7	7
O_3	4	6
NO_2	NA	NA
Cardiovascular deaths		
$PM_{2.5}$	NA	NA
O_3	NA	NA

Distributed lag effect of	Maximum RR at lag	Significant RR up to lag
NO_2	1	1
Nephrological deaths		
$PM_{2.5}$	NA	NA
O_3	0	1
NO_2	0	2

TABLE S10

Percent increase in adjusted mortality risk (and 95% CI) for specific causes of death for a 10 μg m^{-3} change in $PM_{2.5}$, O_3, or NO_2 exposure for Varanasi only

Cause of Death	$PM_{2.5}$		O_3		NO_2	
	% change in mortality		% change in mortality		% change in mortality	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
In-hospital all-cause deaths						
Overall	0.19	(-0.37, 0.76)	10.95	(-6.81, 29.03)	-0.86	(-6.82, 5.13)
Male	**0.85**	**(0.12, 1.59)**	**40.17**	**(16.69, 64.20)**	-5.15	(-13.05, 2.82)
Female	-0.54	(-1.43, 0.35)	-18.96	(-45.37, 8.17)	2.40	(-6.39, 11.26)
Age: <65	-0.21	(-0.91, 0.49)	-1.03	(-22.06, 20.45)	-0.08	(-7.25, 7.14)
Age: >=65	**1.22**	**(0.28, 2.16)**	**42.03**	**(10.69, 74.36)**	-2.00	(-12.13, 8.23)
Winter	-1.01	(-13.01, 11.14)	18.81	(-68.85, 114.71)	3.31	(-8.05, 14.79)
Summer	4.34	(-16.36, 25.48)	-64.01	(-134.62, 12.35)	7.56	(-5.42, 20.72)
Other Seasons	12.28	(-1.41, 26.16)	1.49	(-54.71, 61.02)	4.69	(-2.86, 12.29)
Neurological deaths						
Overall	**3.86**	**(1.78, 5.94)**	8.85	(-4.23, 21.92)	**8.88**	**(0.94, 16.88)**
Male	1.89	(-0.79, 4.58)	11.41	(-0.94, 23.92)	**17.16**	**(6.54, 27.89)**
Female	**6.95**	**(3.31, 10.60)**	**14.72**	**(0.30, 29.36)**	-9.51	(-23.88, 5.07)
Age: <65	**3.92**	**(0.78, 7.07)**	**24.32**	**(11.94, 36.86)**	8.52	(-2.86, 20.02)
Age: >=65	**3.03**	**(0.09, 5.99)**	-0.13	(-14.23, 14.17)	5.61	(-6.61, 17.97)
Winter	NA	NA	NA	NA	NA	NA
Summer	NA	NA	NA	NA	NA	NA
Other Seasons	NA	NA	NA	NA	NA	NA
East UP	NA	NA	NA	NA	NA	NA
West Bihar	NA	NA	NA	NA	NA	NA
Respiratory deaths						
Overall	**1.87**	**(0.22, 3.54)**	**8.98**	**(0.51, 17.45)**	-11.74	(-19.04, -4.39)
Male	1.85	(-0.34, 4.05)	-5.45	(-17.37, 6.62)	-8.05	(-17.89, 1.89)
Female	1.39	(-1.18, 3.97)	**13.90**	**(2.66, 25.13)**	-10.02	(-21.88, 1.99)
Age: <65	0.92	(-1.25, 3.10)	-0.48	(-12.03, 11.21)	-3.98	(-13.31, 5.44)
Age: >=65	**4.42**	**(1.69, 7.15)**	**20.53**	**(4.87, 36.19)**	-27.37	(-40.31, -14.26)
Winter	NA	NA	NA	NA	NA	NA
Summer	NA	NA	NA	NA	NA	NA

Cause of Death	$PM_{2.5}$		O_3		NO_2	
	% change in mortality		% change in mortality		% change in mortality	
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
Other Seasons	NA	NA	NA	NA	NA	NA
East UP	NA	NA	NA	NA	NA	NA
West Bihar	NA	NA	NA	NA	NA	NA
Cardiovascular deaths						
Overall	0.81	(-1.01, 2.64)	4.64	(-2.20, 11.53)	**7.15**	**(0.49, 13.86)**
Male	1.59	(-0.66, 3.84)	**18.53**	**(9.41, 27.73)**	5.69	(-2.93, 14.38)
Female	-0.39	(-3.61, 2.84)	-8.88	(-19.74, 2.09)	5.19	(-5.84, 16.35)
Age: <65	-4.84	(-7.79, -1.88)	**16.36**	**(5.80, 27.02)**	5.56	(-5.22, 16.45)
Age: >=65	**5.24**	**(2.84, 7.64)**	-7.61	(-17.06, 1.93)	**10.74**	**(1.85, 19.71)**
Winter	NA	NA	NA	NA	NA	NA
Summer	NA	NA	NA	NA	NA	NA
Other Seasons	NA	NA	NA	NA	NA	NA
East UP	NA	NA	NA	NA	NA	NA
West Bihar	NA	NA	NA	NA	NA	NA
Nephrological deaths						
Overall	1.80	(-0.46, 4.08)	**11.80**	**(2.65, 21.03)**	**14.73**	**(7.45, 22.07)**
Male	2.21	(-0.64, 5.07)	**14.10**	**(3.11, 25.21)**	**12.94**	**(3.01, 22.97)**
Female	0.94	(-2.82, 4.71)	9.30	(-7.06, 25.94)	**14.99**	**(4.48, 25.60)**
Age: <65	**4.14**	**(1.21, 7.08)**	2.68	(-9.26, 14.76)	5.91	(-2.97, 14.88)
Age: >=65	-0.93	(-4.54, 2.70)	**31.18**	**(16.77, 45.80)**	**29.11**	**(16.22, 42.16)**
Winter	NA	NA	NA	NA	NA	NA
Summer	NA	NA	NA	NA	NA	NA
Other Seasons	NA	NA	NA	NA	NA	NA
East UP	NA	NA	NA	NA	NA	NA
West Bihar	NA	NA	NA	NA	NA	NA

> Values in bold are statistically significant ($p < 0.05$).