Science of the Total Environment 858 (2023) 159634

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

A novel mathematical model for estimating the relative risk of mortality attributable to the combined effect of ambient fine particulate matter ($PM_{2.5}$) and cold ambient temperature

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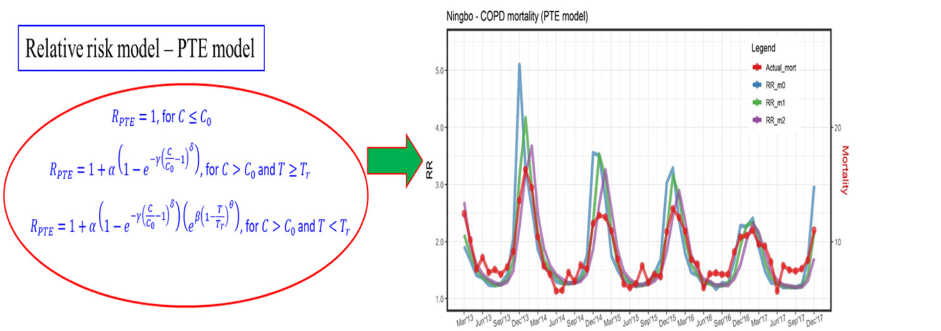
HIGHLIGHTS

- A novel relative risk (RR) of pollutant-temperature exposure (PTE) model is proposed.
- RR is attributable to the combined effect of ambient $PM_{2.5}$ and cold temperature.
- The predictive ability of the PTE model is validated using actual data of Ningbo city.
- The PTE model is found to be able to provide more accurate RR estimates.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Anastasia Paschalidou

Keywords:
Ambient air pollution
Ambient temperature
China
COPD
Pollutant-temperature exposure
Relative risk

ABSTRACT

Exposures to ambient fine particulate matter ($PM_{2.5}$) and cold ambient temperatures have been identified as important risk factors in contributing towards the global mortality from chronic obstructive pulmonary disease (COPD). Despite China currently being the country with the largest population in the world, previous relative risk (RR) models have considered little or no information from the ambient air pollution related cohort studies in the country. This likely provides a less accurate picture of the trend in air pollution attributable mortality in the country over time. A novel relative risk model called pollutant-temperature exposure (PTE) model is proposed to estimate the RR attributable to the combined effect of air pollution and ambient temperature in a population. In this paper, the pollutant concentration-response curve was extrapolated from the cohort studies in China, whereas the temperature response curve was extracted from a study in Yangtze River Delta (YRD) region. The performance of the PTE model was compared with the integrated exposure-response (IER) model using the data of YRD region, which revealed that the estimated relative risks of the PTE model were noticeably higher than the IER model during the winter season. Furthermore, the predictive ability of the PTE model was validated using actual data of Ningbo city, which showed that the estimated RR using the PTE model with 1-month moving average data showed a good result with the trend of actual COPD mortality, indicated by a lower root mean square error (RMSE = 0.956). By considering the combined effect of ambient air pollutant and ambient temperature, the PTE model is expected to provide more accurate relative risk estimates for the regions with high levels of ambient $PM_{2.5}$ and seasonal variation of ambient temperature.

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http://dx.doi.org/10.1016/j.scitotenv.2022.159634
Received 22 August 2022; Received in revised form 17 October 2022; Accepted 18 October 2022
Available online 21 October 2022

1. Introduction

Exposure to ambient fine particulate matter ($PM_{2.5}$) has been extensively studied and identified as an important risk factor for mortality in the Global Burden of Disease (GBD) studies (Lim et al., 2012; Forouzanfar et al., 2016; Murray et al., 2020; Yin et al., 2020). Furthermore, the association between ambient $PM_{2.5}$ and ambient temperature has been analysed in the previous study (Chung et al., 2021), which suggests that higher $PM_{2.5}$ pollutant levels in the atmosphere are often linked to episodes of lower ambient temperature. A potential mechanism behind the association may involve the temperature inversion which most likely traps the atmospheric particulate matter (Li et al., 2015). Xu et al. (2019) reported that 93 % of severe polluted days on which their daily $PM_{2.5}$ exceeded 150 μg/m^3 were related to a temperature inversion, and they often occurred during wintertime. In the GBD study 2019, the risk factor of non-optimal temperature was included for the estimation of attributable mortality for the population around the world (Murray et al., 2020). According to the GBD study 2019, the ambient particulate matter pollution and low non-optimal temperature were ranked as the second and fifth largest contributors of chronic pulmonary obstructive disease (COPD) mortality around the world, respectively. In the previous health assessments, the risk factors of ambient air pollution and ambient temperature were separately estimated and linked with the COPD mortality, despite there is a potential connection between these risk factors. However, this could lead to a less accurate risk estimation for regions with distinct seasons and high pollutant levels.

The quantitative assessment of global health risk attributable to ambient air pollution has become more significant due to the increased level of ambient air pollution since the era of industrialisation. Relative risk (RR) models have been developed and updated over the past few decades to provide a more accurate estimation of disease burden attributable to air pollution around the world. Previous RR models employed linear or log-linear functions for estimating the effect of air pollution ($PM_{2.5}$ and PM_{10} exposure) on different cause groupings for mortality such as all cause, respiratory, and cardiopulmonary (Pope et al., 2002; Ostro et al., 2004). However, these models could lead to a greater degree of uncertainty in relative risk at higher pollutant levels due to the extrapolation of the function beyond PM levels observed in study locations. The linear or log-linear form models were found to be more appropriate to the region with lower $PM_{2.5}$ levels, for example below 50 μg/m^3. The integrated exposure-response (IER) model was established to estimate the RR of cause-specific mortalities such as ischaemic heart disease (IHD), cerebrovascular disease (stroke), chronic obstructive pulmonary disease (COPD), and lung cancer (LC), which allowed non-linear functions over the entire global exposure range of $PM_{2.5}$ (Burnett et al., 2014). The IER model also utilised the information from various $PM_{2.5}$ sources other than ambient air pollution such as second-hand tobacco smoke (SHS), household air pollution (HAP), and active smoking (AS). The development of IER model relied on the RR information based on the studies in North America and European countries, which often resulted in a less accurate estimation in Asian countries such as India and China (Pope et al., 2018). A recent RR model called global exposure mortality model (GEMM) employed the information of outdoor air pollution based on the 41 cohort studies which were mostly conducted in North America and European countries (Burnett et al., 2018). The GEMM relaxed many assumptions of the IER model and included a Chinese cohort study conducted by Yin et al. (2017) to expand the range of $PM_{2.5}$ exposure in their study. Furthermore, the association of $PM_{2.5}$-mortality in each cohort study has been described by a hazard ratio function which can capture a variety of shapes such as linear, log-linear, and threshold (Nasari et al., 2016; Burnett et al., 2018). These made the GEMM less uncertain in estimating the relative risk of noncommunicable disease (NCD) and lower respiratory infection (LRI) attributable to ambient $PM_{2.5}$. However, the GEMM did not consider other possible risk factors contributing to the additional risk of the disease burden.

Several identified factors may lead to a greater uncertainty in the estimation of relative risk attributable to air pollution in China. Firstly, previous models have considered little or no RR information from Chinese cohort studies. The extrapolation of RR function using the previous models may result in greater uncertainty in estimating mortality risk for China. Secondly, most of the previous models tend to be more applicable to regions of low pollutant levels, for example North America and European countries. Thirdly, the effect of ambient temperature may significantly modify the attributable risk of mortality due to ambient $PM_{2.5}$ (Sun et al., 2015; Ji et al., 2020) and therefore needs to be considered during the estimation of relative risk. To address the limitations of the previous RR models, a novel RR model called pollutant-temperature exposure (PTE) was employed in the current study to improve the estimation of mortality risk attributable to the combined effect of ambient $PM_{2.5}$ and cold ambient temperature. The objectives of this study are (1) to establish a novel relative risk model called PTE model which takes into considerations the combined effect of ambient $PM_{2.5}$ and cold ambient temperature; (2) to evaluate the performance of the PTE model using data of Chinese cities; (3) to improve the estimation of relative risk of COPD mortality using the PTE model.

2. Methodology

2.1. Key assumptions in the model

In this study, the relative risk (RR) model of COPD mortality attributable to the combined effect of ambient $PM_{2.5}$ and cold ambient temperature is proposed and developed based on the following assumptions:

(1) The combined effect of risk factors is multiplicative. Exposures to higher $PM_{2.5}$ concentration and lower ambient temperature are associated with a higher mortality risk of COPD. Ambient particulate matter and low non-optimal ambient temperature have been identified as risk factors of COPD mortality in the GBD study 2019 (Murray et al., 2020).
(2) The source of $PM_{2.5}$ is only restricted to ambient air pollution (AAP). Although other $PM_{2.5}$-related risk factors such as HAP, SHS, and AS have been associated with increased attributable mortality, it is advisable to only consider a specific source in the model because the toxicity and exposure pattern of those sources may differ from each other.
(3) The individual associations between $PM_{2.5}$ exposure and RR of attributable mortality, and between exposure to low ambient temperatures and RR of attributable mortality are not limited to linear form of function (Burnett et al., 2014).
(4) The effects of hot ambient temperature on attributable mortality are relatively insignificant as compared to cold ambient temperature (Gasparrini et al., 2015; Chen et al., 2018; Liu et al., 2020; Murray et al., 2020; Gasparrini et al., 2022). Gasparrini et al. (2015) reported that the attributable mortality caused by cold ambient temperature (7.29 %) was greater than by hot ambient temperature (0.42 %) in all study regions, including China. Therefore, the estimation of relative risk using the PTE model only considers the effects of cold ambient temperatures that are lower than the selected reference temperature.

2.2. Relative risk model – PTE model

The pollutant-temperature exposure (PTE) model is regarded as a modified version of the integrated exposure-response (IER) model, which considers the effects of both ambient $PM_{2.5}$ and cold ambient temperature on disease burden, for instance COPD mortality. The PTE model describes the relative risk of disease burden across a wide range of ambient $PM_{2.5}$ pollutant concentration and cold ambient temperature in any given population. The mathematical form of the PTE model is shown by Eqs. (1) to (3):

$$R_{PTE} = 1, \text{ for } C \le C_0 \tag{1}$$

$$R_{PTE} = 1 + \alpha\left(1 - e^{-\gamma\left(\frac{C}{C_0}-1\right)^{\delta}}\right), \text{for } C > C_0 \text{ and } T \ge T_r \tag{2}$$

$$R_{PTE} = 1 + \alpha \left(1 - e^{-\gamma\left(\frac{C}{C_0} - 1\right)^{\delta}}\right)\left(e^{\beta\left(1 - \frac{T}{T_r}\right)^{\theta}}\right), \text{for } C > C_0 \text{ and } T < T_r \quad (3)$$

where C represents the ambient $PM_{2.5}$ exposure in the unit of μg/m^3 and T represents the ambient temperature in the unit of °C. C_0 is the counterfactual concentration of $PM_{2.5}$ and T_r is the reference temperature of any given location in which there are no harmful impacts only when $T \geq T_r$ and $C \leq C_0$. Under the condition of $T \geq T_r$, RR of attributable mortality only depends on the effect of ambient $PM_{2.5}$ exposure, as described by Eq. (2). The expression of the PTE model under the condition $T \geq T_r$ looks similar with the previous IER model, as shown in Eq. (4). Nevertheless, the PTE model consists of 5 coefficients, which determines the shape of each risk-outcome association. γ and δ coefficients affect the model behaviour based on the effect of ambient $PM_{2.5}$ exposure, β and θ coefficients control the curvature with respect to the effect of temperature exposure, and α coefficient adjusts the combined effect of ambient $PM_{2.5}$ and temperature on the PTE model.

$$R_{IER} = 1 + \alpha\left(1 - e^{-\gamma(C - C_0)^{\delta}}\right) \quad (4)$$

The counterfactual concentration of $PM_{2.5}$ was assumed to be 5 μg/m^3 in this study, which is within the range of uniform uncertainty distribution (2.4–8.8 μg/m^3) employed by most of the previous studies. The reference temperature in the PTE model is specific to geographical location and type of disease burden. The reference temperature of COPD mortality in Yangtze River Delta was selected as 25 °C. All the unknown coefficients (α, β, γ, δ, θ) in the PTE model were estimated based on the actual data of pollutant concentration, temperature, and mortality in the study region.

In establishing the PTE model, all the necessary information of RR estimate on the cause-specific mortality across the $PM_{2.5}$ exposure range were extracted from a pooled risk estimate (Chung et al., 2022), which included the relevant Chinese cohort studies that studied the association between $PM_{2.5}$ and COPD mortality (Wong et al., 2015; Yin et al., 2017; Yang et al., 2018). These Chinese cohort studies employed a Cox proportional hazards regression model and a relatively wider range of ambient $PM_{2.5}$ exposure over the population as compared to those studies conducted in North America or European countries. The RR information of ambient temperature exposure for the PTE model was also derived from a study in Yangtze River Delta (YRD) of China, which is known as one of the most densely populated regions in the world.

2.3. Verification and validation of relative risk model

The verification of the PTE model was performed by comparing the RR result with the estimation of the IER model. The pollutant and temperature data of Ningbo and Hangzhou from 2013 to 2017 were collected and used in this study. The IER model, as represented by Eq. (4), only takes the single effect of $PM_{2.5}$ concentration when estimating the relative risk of disease burden such as COPD mortality. The unknown coefficients (α, γ, δ) in the IER model were estimated by using a similar method to ensure a reliable comparison on the RR estimates in both PTE and IER models. To better illustrate the seasonal variation of RR values predicted from the temperature effect of the PTE model, the monthly average data of ambient $PM_{2.5}$ concentration and ambient temperature were stratified into four seasons: winter (from December to February), spring (from March to May), summer (from June to August), and autumn (from September to November).

The validation of the PTE model was performed by employing the actual data in YRD region of China. The data of COPD mortality in Ningbo from 2013 to 2017 were collected and used in this study. To investigate the variation of the combined effect of $PM_{2.5}$ and temperature, the monthly average data of ambient $PM_{2.5}$ and ambient temperature in Ningbo were used to estimate the RR using the PTE model. Furthermore, different moving average data of $PM_{2.5}$ and temperature, including 0-month (m0), 1-month (m1), and 2-month (m2), were also calculated and used for the comparison between RR estimates and actual COPD mortality data. The relationships between RR estimates using different moving average data and actual COPD mortality were plotted and analysed. Furthermore, a linear relationship between mortality and the inverse of relative risk is observed, as indicated in Eq. (5):

$$M = P \times I \times \left[1 - \frac{1}{R}\right] \quad (5)$$

where M represents the estimated mortality. P is the study population and I is the baseline mortality rate. R is the relative risk estimated using either the PTE or IER models. By employing a linear regression model, the value of root mean square error (RMSE) was used to indicate the difference between actual mortality and fitted mortality using the PTE and IER models with different moving average data. A lower RMSE value indicates a better relative risk model, which could predict more accurately the mortality.

2.4. Uncertainty analysis

In the PTE model, the estimates of counterfactual concentration (C_0) and reference temperature (T_r) may affect the ultimate prediction of RR result, especially under the extreme conditions, such as low pollutant concentration and low ambient temperatures. Different values of the counterfactual concentration from 3 to 7 μg/m^3 were explored in the PTE model to investigate the ability of the model to describe uncertainty in the shape at low pollutant concentration.

The reference temperature of the PTE model is intended to be specific for each type of disease burden and geographic location as they may respond differently to the population with respect to regional ambient temperature. The current study selected a reference temperature of 25 °C based on the average value of daily ambient temperature for which the 5th percentile of COPD mortality distribution in Ningbo was observed. This also implies that a minimum impact of ambient temperature on the mortality risk was typically observed at the selected reference temperature. Ma et al. (2015) employed the 75th percentile of temperature distribution as the reference temperature in their study. Different reference temperatures from 21 to 27 °C were applied to the PTE model to study the effect of reference temperature in the resulting relative risk.

3. Results

3.1. Characteristics of the PTE model

The estimates of relative risk (R_{PTE}) based on the combined effect of ambient $PM_{2.5}$ concentration and ambient temperature on COPD mortality are shown in Fig. 1. The disease-specific and location-specific PTE model allows the prediction of RR that considers the modifying effect of ambient temperature on the disease burden in the population. Furthermore, with respect to pollutant effect, the RR estimates of the PTE model increase in a supra-linear pattern with pollutant concentration, as the curves tend to flatten out at high pollutant concentration when ambient temperature is not extremely low. On the other hand, temperature effect modifies the exposure-response curve for the RR estimation. An inverse J-shaped curve is well observed for each constant pollutant concentration when ambient temperature slowly decreases. This also demonstrates that the exponential growth of the exposure-response curve at extreme low temperatures could amplify the effect of air pollution on each type of disease burden.

Fig. 2 shows the contour plot of predicted RR values of COPD mortality attributable to the effects of ambient $PM_{2.5}$ and ambient temperature. The counterfactual concentration of $PM_{2.5}$ was chosen as 5 μg/m^3 in the current study. This also suggests that the relative risk equals 1 when the observed pollutant concentration is less than 5 μg/m^3 in the PTE model. The reference temperature of minimum COPD mortality in YRD was selected as 25 °C in the current study. This implies that the attributable relative risk for each mortality only relies on pollutant concentration effect when the observed temperature is above the reference temperature in the PTE model.

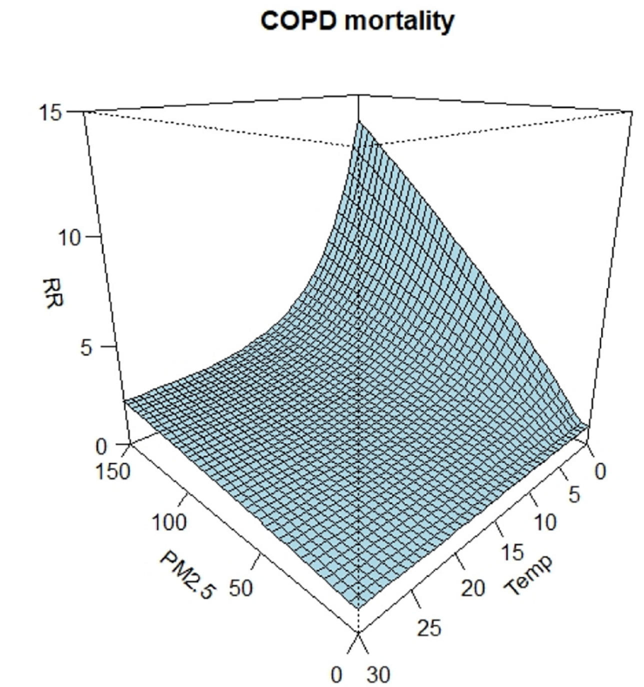

Fig. 1. 3-Dimensional plot of predicted relative risk (RR) values for attributable mortality of COPD due to the combined effect of ambient $PM_{2.5}$ concentration and ambient temperature.

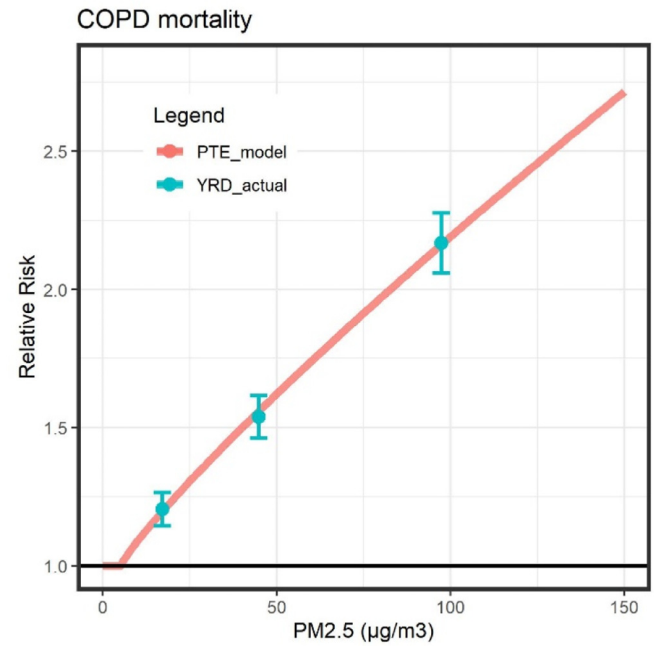

Fig. 3. Pollutant effect of the PTE model by fitting it with the information of Chinese cohort studies at annual mean temperature of 17 °C.

The behaviours of the fitted PTE model with respect to pollutant effect and temperature effect are shown in Figs. 3 and 4, respectively. Three different points of pollutant concentration were selected for the model fitting, including the mean value (44.8 μg/m^3), 5th percentile (17.1 μg/m^3), and 95th percentile (97.3 μg/m^3) of $PM_{2.5}$ distribution in Ningbo across the study period. The corresponding RR information was extracted and extrapolated from Chinese cohort studies (Wong et al., 2015; Yin et al., 2017; Yang et al., 2018), which studied long-term exposure to particulate matter on the population over 10 years. When selecting the suitable model coefficients (α, β, γ, δ, θ) of the PTE model for each type of disease burden, the pollutant concentration-response curve must fulfil the requirements of being fitted with the actual RR values at the corresponding concentrations. In the current study, only errors within 5 % of the measured RR values were allowed in the fitting process of the PTE model, which are plotted as blue error bars in Fig. 3. Furthermore, the selection of model coefficients also relies on the temperature curve which shows the values of RR at different temperature with respect to RR at reference temperature. In Fig. 4, RR at reference temperature was set to 1, and relative RRs were plotted and compared with the actual relative RR at Yangtze River Delta. The model coefficient β controls the magnitude of amplified relative risk at lower

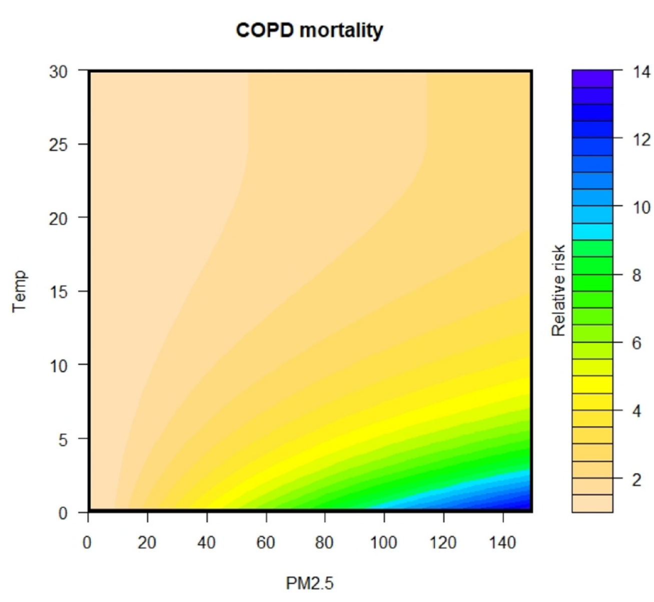

Fig. 2. Contour plots of predicted relative risk (RR) values for COPD mortality with respect to the combined effect of ambient $PM_{2.5}$ concentration and ambient temperature.

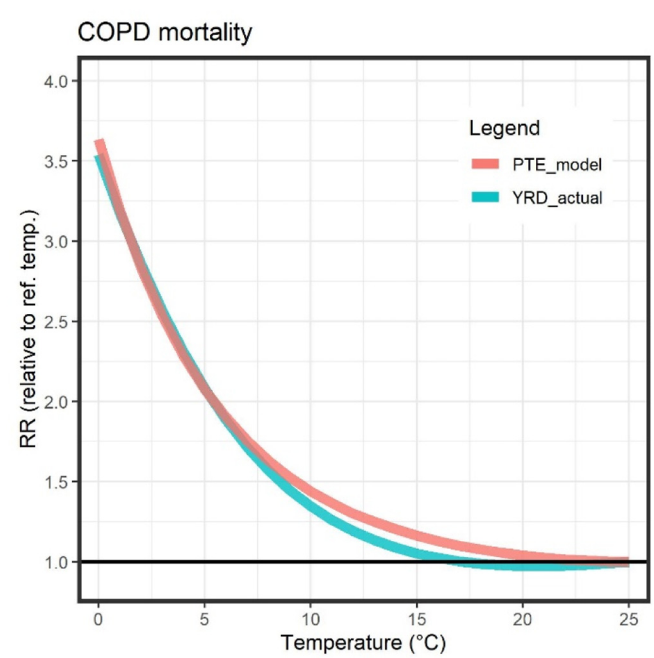

Fig. 4. Temperature effect of the PTE model by fitting it with the information of YRD data at annual mean $PM_{2.5}$ concentration of 44.8 μg/m^3.

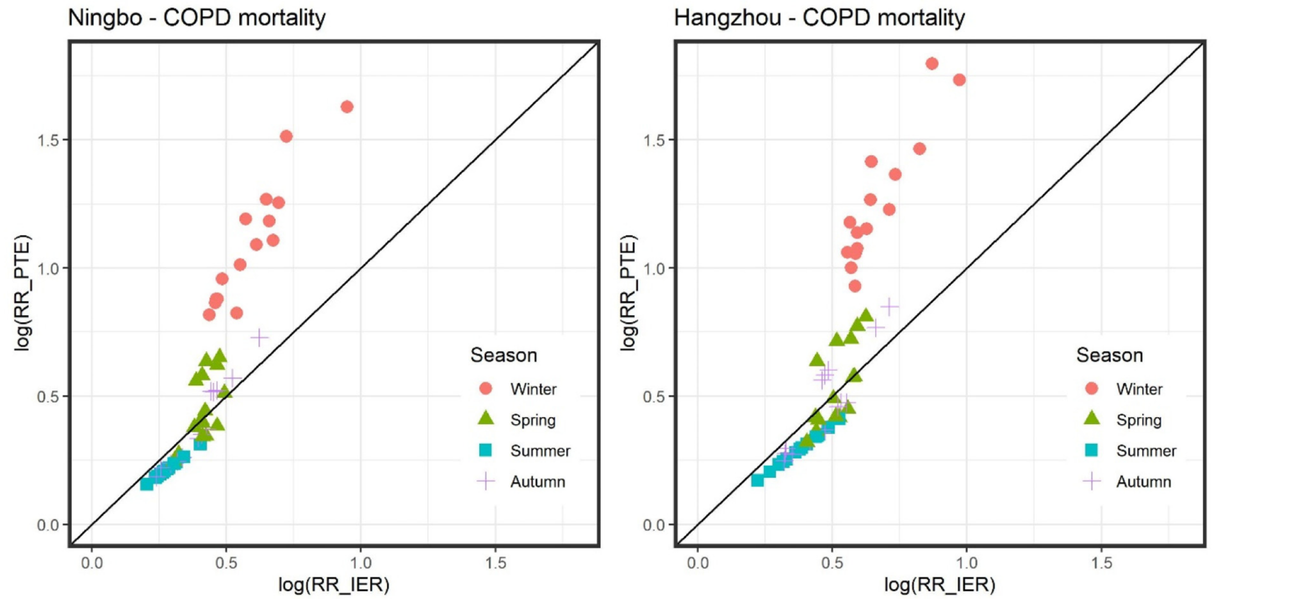

Fig. 5. Seasonal specific estimates of relative risk (RR) of COPD mortality by the PTE model and IER model using the data of Ningbo (left) and Hangzhou (right), respectively. (Straight line represents 1:1 association.)

temperatures, whereas θ adjusts the degree of curvatures in the temperature curve.

3.2. Verification and validation of the PTE model

The monthly average data of pollutant and temperature in Ningbo and Hangzhou were used for the verification of the PTE model by comparing the RR estimates with the IER model. The comparison between the RR estimates from the PTE and IER models based on the data of Ningbo and Hangzhou were shown in Fig. 5. Each individual point represents predicted RR value using the PTE and IER models in a monthly basis. For COPD mortality, the comparison of RR values predicted by the PTE and IER models in each season behaved differently in both cities of Ningbo and Hangzhou. In summer, the RR estimates were generally lower in the PTE model when compared to the IER model. The difference in RR estimates by two models was noticeable in winter as the PTE model tended to estimate higher RR values. However, there were no distinct patterns for the comparison of RR estimates during spring and autumn in which the change of temperature profiles was more unpredictable in these seasons over the years.

The predictive performance of the PTE model was compared with actual COPD mortality using three different exposure measurements, including 0-month (m0), 1-month (m1), and 2-month (m2) moving average data of $PM_{2.5}$ and ambient temperature. Figs. 6 and 7 illustrate the comparison between RR estimates using different moving average data and actual mortality of COPD in Ningbo based on the PTE and IER models, respectively. For COPD mortality, similar trends were observed over time on both RR

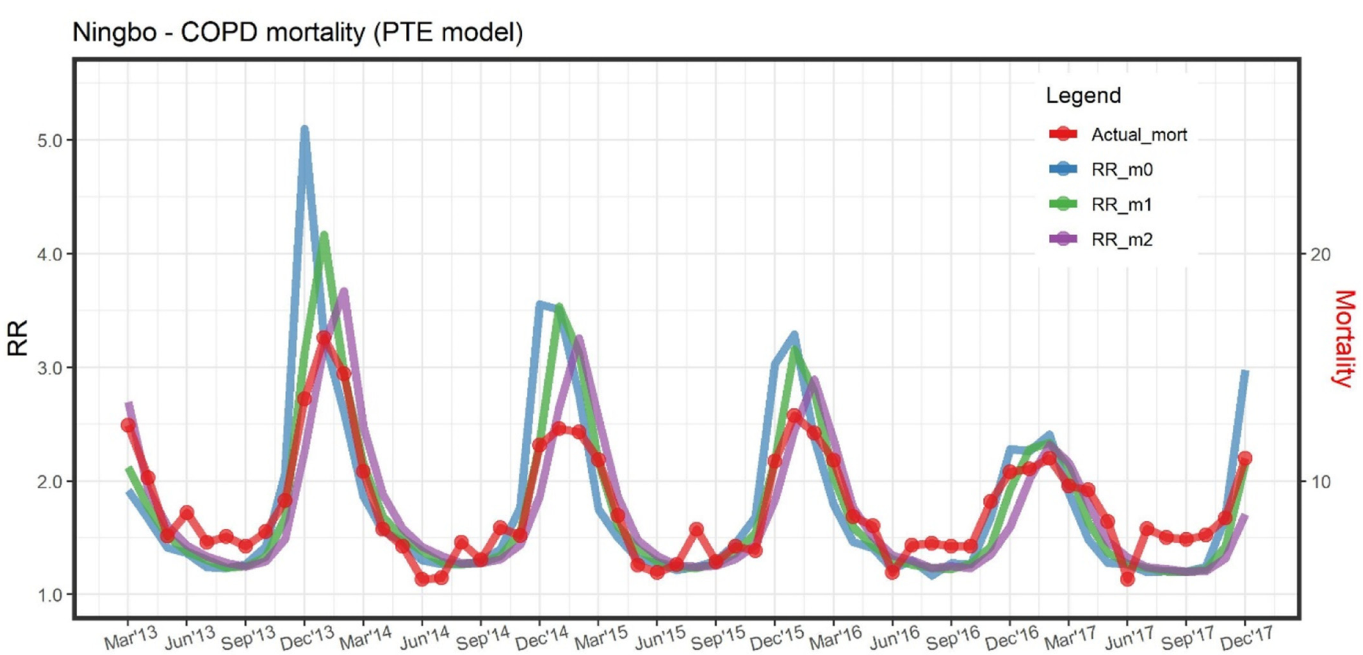

Fig. 6. Association between RR estimates of the PTE model with different moving average data and actual COPD mortality (red line, secondary axis) in Ningbo.

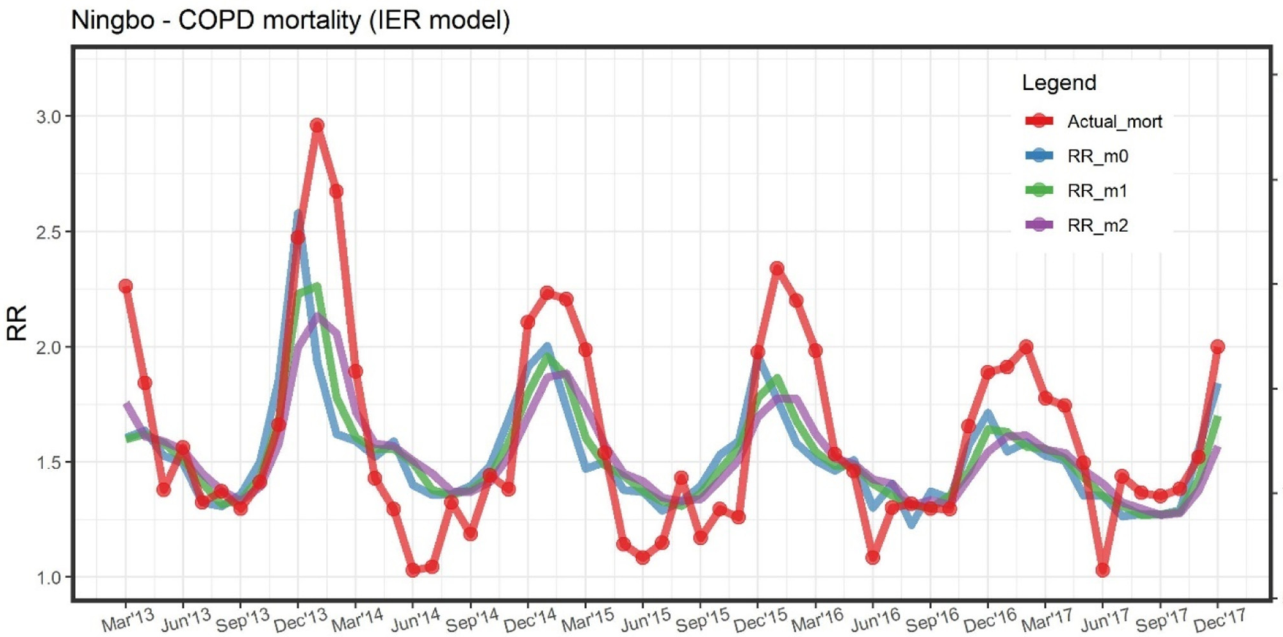

Fig. 7. Association between RR estimates of the IER model with different moving average data and actual COPD mortality (red line, secondary axis) in Ningbo.

estimates using the PTE model and actual mortality, especially for the peaks where ambient $PM_{2.5}$ level was highest and ambient temperature was lowest throughout the year. Furthermore, by observing Figs. 6 and 7, the RR estimates of both models with 0-month (m0) moving average data showed the least promising result when they were compared with the actual COPD mortality data in Ningbo. This suggests that both pollutant and temperature data in the current month are not adequate to provide an accurate RR estimate in the current month.

The comparison of RMSE between actual mortality and fitted mortality using the PTE and IER models is summarised in Table 1. Overall, the PTE model using 1-month (m1) moving average data generated a better prediction result, as it employed the pollutant and temperature data in both previous month and current month for the prediction of relative risk in the current month. The result might suggest a possible exposure period for the effect of pollutant-temperature interaction on COPD mortality to take place. Out of all exposure data, the PTE model generally produced a better fit with actual COPD mortality data, suggesting a better predictive ability of relative risk as compared to the IER model. Furthermore, the result also indicated that 1-month (m1) moving average data of ambient $PM_{2.5}$ concentration and ambient temperature also improved the PTE prediction result with the lowest RMSE of 0.956.

3.3. Uncertainty analysis

Different counterfactual concentrations of $PM_{2.5}$ were chosen to study their potential effect on the PTE model for the uncertainty analysis. Table 2 describes the percentage of errors between the measured and predicted RRs based on the selection of different counterfactual concentrations in the PTE model. The value of counterfactual concentration affected the estimation of the unknown coefficients in the PTE model, which eventually altered the RR prediction result. For COPD mortality, the counterfactual concentration of 5 $\mu g/m^3$ was found to be a better option as it resulted in less percentage of error on the RR information between the cohort studies and the estimated RR values.

Additionally, using the PTE model, different reference temperatures were employed to analyse their effect towards the estimated relative risk. Fig. 8 displays the relative risk profiles at constant pollutant concentration ($C = 44.8\ \mu g/m^3$) with respect to different reference temperatures selected in the PTE model. When the temperatures were above the selected reference temperature in the PTE model, the relative risks were only attributable to the effect of pollutant concentration, which contributed to the same value of relative risk ($R = 1.42$). Fig. 9 shows the relative risk profiles with respect to different reference temperatures selected in the PTE model. The relative risk did not change significantly by selecting a different reference temperature, however, it tended to decrease by selecting a lower reference temperature.

4. Discussion

A novel relative risk (RR) model called pollutant-temperature exposure (PTE) was developed in the current study by employing the Chinese cohort studies that provided the evidence of ambient air pollution-related disease burden over a wide range of ambient fine particulate matter ($PM_{2.5}$) exposure and ambient temperature exposure. Exposures to high level of ambient $PM_{2.5}$ and low non-optimal ambient temperature have been associated to increased risk of attributable mortalities such as chronic obstructive pulmonary disease (COPD). At a constant ambient temperature, the sublinear pollutant concentration-response curve estimates the relative risk with respect to the increased pollutant level, as shown in Fig. 3. Furthermore, at a constant pollutant concentration, the inverse J-shaped temperature response

Table 1
RMSE between the actual COPD mortality data in Ningbo and the predicted mortality using the estimated RRs of the PTE and IER models.

Exposure data	PTE model	IER model
moving_0 (m0)	1.151	1.596
moving_1 (m1)	0.956	1.307
moving_2 (m2)	1.193	1.243

Table 2
Uncertainty analysis on the selection of different counterfactual concentrations in the PTE model.

Counterfactual concentration ($\mu g/m^3$)	Error (%) in RR estimates
3	1.5
5	1.3
7	1.7

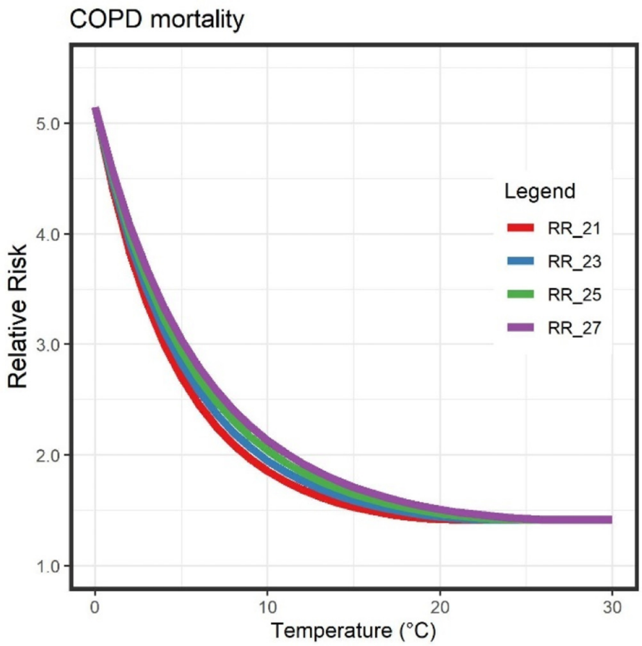

Fig. 8. The effect of reference temperature on the relative risk profile at the constant pollutant concentration ($C = 44.8\ \mu g/m^3$).

curve provides the relative risk with respect to the effect of ambient temperature, as shown in Fig. 4. When ambient temperature is below the reference temperature of a particular disease, the RR attributable to pollutant exposure is modified by the temperature effect in the PTE model. Conversely, when ambient temperature is above the reference temperature, the RR values solely depend on the pollutant exposure.

The relationship between long-term exposure to ambient $PM_{2.5}$ and COPD mortality in China was studied and analysed in the previous studies (Wong et al., 2015; Yin et al., 2017; Yang et al., 2018), which reported a pooled risk value of 1.12 (95 % CI: 1.11–1.13) per 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration (Chung et al., 2022). The cohort study by Yin et al. (2017) played a major role in providing the evidence of the effect of ambient $PM_{2.5}$ on COPD mortality in Chinese population, as it involved a large study population of 189,793 people over the study period more than 10 years and considered different types of exposure assessment including satellite-based, chemical transport model, and air monitoring station. Furthermore, the information of temperature response curve in Ningbo was consistent with the previous studies (Ding et al., 2015; Yang et al., 2015), which reported an inverse J-shaped curve for the association between exposure to ambient temperature and relative risk at a constant $PM_{2.5}$ concentration.

The PTE model serves as an advanced version of the RR model, which addresses some of the limitations of the IER model. When integrating the IER model, the RR information of sources other than ambient air pollution was included, for example, active smoking, household air pollution, and second-hand tobacco smoke (Burnett et al., 2014). These led to the assumption made in the IER model, which did not consider the difference in toxicity of $PM_{2.5}$ based on the emission sources. In addition, the RR information of ambient air pollution was only a small portion of the total information constructing the IER model, for example, only 3 out of 15 total RR estimates were used to represent the information of COPD mortality attributable to the effect of ambient air pollution. In contrast, the PTE model only employed the cohort studies of ambient air pollution to generate the pollutant exposure curve, which relaxed the assumption of toxicity of $PM_{2.5}$ in different emission sources. The PTE model also addresses the limitation of previous RR models, which assumes no interaction among the different exposure sources for disease burden. The potential interaction between ambient $PM_{2.5}$ and ambient temperature could affect the estimation of actual RR, which might therefore contribute to uncertainty in quantifying the attributable mortality in the health risk assessment. By separating each risk factor in the estimation, it is likely to inaccurately predict the total disease burden, as the estimation ignores the combined effect of these two risk factors. In the current study, the performance of PTE and IER models were compared by using the monthly average data in YRD region of China, as shown in Fig. 5. The differences in RR estimates between two models were found to be largest during wintertime, thus implying that the PTE model is able to estimate the RR attributable to the temperature effect. The seasonal variation of pollutant concentration and temperature might play important roles in estimating the pattern of attributable mortality over time.

One of the important implications of the PTE model was that the estimation of RR using 1-month moving average data for COPD mortality showed a better result with the actual mortality data in Ningbo, as illustrated in Fig. 6. The PTE model performed better than the IER model for predicting the trend of actual COPD mortality over the study years in Ningbo, with the lower RMSE observed between actual mortality and fitted mortality using the RR estimates. Furthermore, the PTE model relied on the information of Chinese cohort studies that only considered the effect of ambient $PM_{2.5}$ on disease burden such as COPD. The average exposure levels of ambient $PM_{2.5}$ in the cohort studies were ranged between 33 and 46 $\mu g/m^3$, which were relatively higher than those in the IER model. The PTE model did not require the property of the IER model that flattens out at high $PM_{2.5}$ concentration, since IER model needed to consider the additional information of the association between IHD mortality and smoking intensity in the previous study (Pope et al., 2009). Therefore, the PTE model is expected to be estimating a more accurate RR information of mortality attributable to ambient $PM_{2.5}$, especially at high exposure level.

Other than the comparison between different relative risk models, different exposure measurement of ambient $PM_{2.5}$ concentration and ambient temperature were also explored in the current study, by using the data of current month (m0), 1-month moving average data (m1), and 2-month moving average data (m2). The result showed that the data of current month were not the best measurement for an accurate RR estimation using either the PTE or IER models. Instead, the PTE model with 1-month moving average data was likely to provide more accurate RR estimates, which helped to improve the mortality estimation (RMSE = 0.956). This also indicated that the model estimates might yield a better result by improving the other factors such as the measurement of ambient $PM_{2.5}$ concentration and ambient temperature in the region. The uncertainty analysis explored the selection of different $PM_{2.5}$ counterfactual concentration in the PTE model from 3 to 7 $\mu g/m^3$ and reported that the counterfactual concentration of 5 $\mu g/m^3$ resulted in a least error in the RR estimates. In addition, the uncertainty analysis also studied the effect of different reference temperatures from 21 to 27 °C in the PTE model and reported that the resulting relative risk profiles were similar. However, by lowering the value of reference temperature, it is likely to reduce the relative risks, given the same exposures of ambient $PM_{2.5}$ concentration and ambient temperature. As the selection of reference temperature in the PTE model is specific to location and type of disease burden, it is always recommended to consider both temperature distribution and mortality distribution in the study region when selecting a more suitable reference temperature for the estimation of relative risk using the PTE model.

The current study has several clinical and public health implications. Firstly, the novel PTE model considers the risk factors of ambient $PM_{2.5}$ exposure and cold ambient temperature in the study region. Besides the effect of ambient $PM_{2.5}$ exposure, it is important to include the effect of ambient temperature in a novel risk model as it provides another significant information regarding the effect of climate change on the disease burden. To provide an up-to-date association between climate change and disease burden, the PTE model potentially serves as one of the key steps in the management of the adverse health effects of climate change (Costello et al., 2009). Secondly, the development of the PTE model also provides a new insight into the environmental health risk model that considers the combined effect of multiple environmental risk factors. The PTE model also addresses the significance of a better mathematical model for evaluating the air

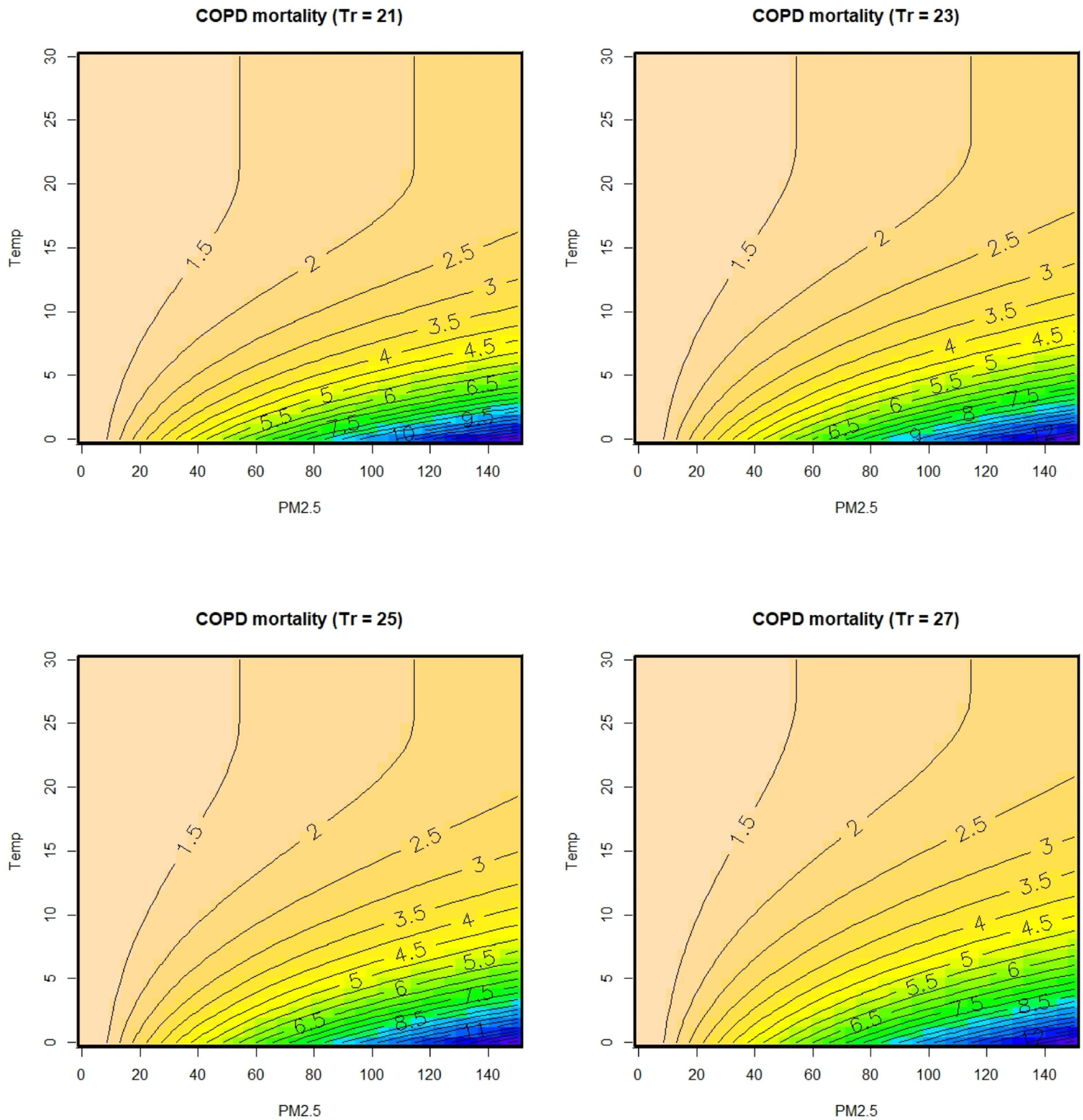

Fig. 9. Contour plots of predicted relative risk (RR) values for COPD mortality for difference reference temperatures at 21 °C (top left), 23 °C (top right), 25 °C (bottom left), and 27 °C (bottom right).

pollution-health association, as well as the climate-health association in the current and future environmental health risk assessment. Thirdly, the PTE model potentially works as a forecast model to estimate the mortality risk attributable to the combined effect of ambient $PM_{2.5}$ and cold ambient temperature in a specific region, especially in the healthcare facilities where most of the vulnerable population are located. The elderly population tends to be more susceptible to exposures such as high levels of ambient $PM_{2.5}$ (Shumake et al., 2013) and cold ambient temperature (Son et al., 2011). By monitoring the estimated mortality risk from a RR model such as PTE model, it is recommended to include both ambient $PM_{2.5}$ exposure and outdoor cold exposure in the routine clinical practice, which might help to reduce the disease burden, including mortality and morbidity attributable to the combined effect of ambient $PM_{2.5}$ and cold ambient temperature, especially in the management of COPD patients.

Most of the previous ambient air pollution-related RR models have been developed for estimating five cause-specific mortalities, including, COPD, LC, IHD, stroke, and LRI (Burnett et al., 2014; Chowdhury and Dey, 2016; Burnett et al., 2018). In the current study, only COPD mortality were extensively studied and employed for the development of the PTE model. Although this resulted in a better prediction for COPD mortality, it might potentially limit the application of the PTE model in estimating other types of disease burdens. Future works are recommended to explore the application of the PTE model in estimating other disease burdens such as LC, IHD, stroke, and LRI. Furthermore, the hot temperature effect was neglected during the development of the PTE model, as the hot temperature effect is relatively smaller than cold temperature effect. However, it is recommended to include the hot temperature effect in the future development of a climate-sensitive health risk model, especially for the risk estimation during heat waves where a significant effect of hot ambient temperature on mortality is typically observed (Gasparrini et al., 2012; Son et al., 2012). This risk model would benefit the management of health effects of climate change, including global warning, heat waves, cold waves, and extreme weather events.

5. Conclusion

In summary, the pollutant-temperature exposure (PTE) model was demonstrated as an advanced relative risk (RR) model to consider the combined effect of ambient fine particulate matter ($PM_{2.5}$) and cold ambient temperature. In this paper, the PTE model addressed and relaxed some of the limitations in the previous RR models, including the IER model. The comparison of RR estimates between the PTE and IER models suggested that the PTE model performed better than the IER model, especially during winter period when low ambient temperatures were observed. The prediction of RR values for chronic obstructive pulmonary disease (COPD) mortality using the PTE model with 1-month moving average data showed a good fitting result with actual mortality data. The development of the PTE model is particularly beneficial for the regions with high levels of ambient $PM_{2.5}$ and seasonal variation of ambient temperature as it aims to provide a more accurate RR attributable to the combined effect of ambient $PM_{2.5}$ and cold ambient temperature.

Abbreviations

AAP	Ambient air pollution
AS	Active smoking
COPD	Chronic obstructive pulmonary disease
GBD	Global Burden of Disease
HAP	Household air pollution
IER	Integrated exposure-response
IHD	Ischaemic heart disease
LC	Lung cancer
LRI	Lower respiratory infection
NCD	Noncommunicable disease
$PM_{2.5}$	Particles with an aerodynamic diameter of equal or less than 2.5 μm
PTE	Pollutant-temperature exposure
RR	Relative risk
SHS	Second-hand tobacco smoke
YRD	Yangtze River Delta

CRediT authorship contribution statement

Chee Yap Chung: Mathematics model, data curation, methodology, writing- original draft preparation. **Jie Yang:** Project supervision, methodology, conceptualization, manuscript writing-reviewing and editing, modelling. **Xiaogang Yang:** Supervision, Conceptualization, methodology, mathematics model, writing- reviewing and editing. **Jun He:** Supervision, data curation.

Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study was financially supported by the National Natural Science Foundation of China (grant no. 21750110446). The authors would like to thank Ningbo Environmental Monitoring Centre (Ningbo EMC) and Ningbo Centre for Disease Control and Prevention (Ningbo CDC) for sharing the data. Chung C. Y. was supported by the Faculty of Science and Engineering PhD scholarship (Ref No. 19073FOSE) at University of Nottingham Ningbo China (UNNC).

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