Interactive effects of ambient fine particulate matter and ozone on daily mortality in 372 cities: two stage time series analysis

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ABSTRACT

OBJECTIVE
To investigate potential interactive effects of fine particulate matter ($PM_{2.5}$) and ozone (O_3) on daily mortality at global level.

DESIGN
Two stage time series analysis.

SETTING
372 cities across 19 countries and regions.

POPULATION
Daily counts of deaths from all causes, cardiovascular disease, and respiratory disease.

MAIN OUTCOME MEASURE
Daily mortality data during 1994-2020. Stratified analyses by co-pollutant exposures and synergy index (>1 denotes the combined effect of pollutants is greater than individual effects) were applied to explore the interaction between $PM_{2.5}$ and O_3 in association with mortality.

RESULTS
During the study period across the 372 cities, 19.3 million deaths were attributable to all causes, 5.3 million to cardiovascular disease, and 1.9 million to respiratory disease. The risk of total mortality for a 10 µg/m³ increment in $PM_{2.5}$ (lag 0-1 days) ranged from 0.47% (95% confidence interval 0.26% to 0.67%) to 1.25% (1.02% to 1.48%) from the lowest to highest fourths of O_3 concentration; and for a 10 µg/m³ increase in O_3 ranged from 0.04% (−0.09% to 0.16%) to 0.29% (0.18% to 0.39%) from the lowest to highest fourths of $PM_{2.5}$ concentration, with significant differences between strata (P for interaction <0.001). A significant synergistic interaction was also identified between $PM_{2.5}$ and O_3 for total mortality, with a synergy index of 1.93 (95% confidence interval 1.47 to 3.34). Subgroup analyses showed that interactions between $PM_{2.5}$ and O_3 on all three mortality endpoints were more prominent in high latitude regions and during cold seasons.

CONCLUSION
The findings of this study suggest a synergistic effect of $PM_{2.5}$ and O_3 on total, cardiovascular, and respiratory mortality, indicating the benefit of coordinated control strategies for both pollutants.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Short term exposure to ambient fine particulate matter ($PM_{2.5}$) and ozone (O_3) has been linked to increased mortality, but studies evaluating interactive effects have been limited

Studies mostly have been conducted in a single city or country and adopted various designs and model variables, leading to heterogeneous results

WHAT THIS STUDY ADDS

This study found statistically significant synergistic associations between $PM_{2.5}$ and O_3 and total, cardiovascular, and respiratory mortality

The synergistic interactions between $PM_{2.5}$ and O_3 were more prominent in high latitude regions and during cold seasons

Introduction

Numerous epidemiological studies have reported the adverse effects of exposure to ambient air pollution on human health, such as premature mortality and morbidity from major cardiopulmonary diseases.[1-4] Among all air pollutants, fine particulate matter ($PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 µm) and ozone (O_3) are among the most studied, given their harmful impacts on human health and high levels in many parts of the world. Additionally, these are the only two air pollutants included in the Global Burden of Disease study as independent risk factors for mortality in humans.[5] As reported by the Global Burden of Disease 2019 study, exposure to ambient $PM_{2.5}$ and O_3 accounted for 4.1 million and 0.36 million attributable deaths globally in 2019.[6] Although abundant evidence links $PM_{2.5}$ and O_3 with human health outcomes,[7 8] studies have mostly treated the health impacts of $PM_{2.5}$ or O_3 separately, and sometimes they consider the other pollutant as a potential confounder while neglecting potential interactive effects. Experimental studies have proposed the biological plausibility of the combined effects of $PM_{2.5}$ and O_3 through pathways involving lung inflammation, oxidative stress, macrophage activity, and endothelial function.[9] Considering the substantial disease burden attributable to these two air pollutants, it is of great scientific and public health importance to determine whether they have an interactive relationship. Understanding these interactive effects should provide

a scientific knowledge base to incentivise governments to develop strategies on coordinated control of these two important air pollutants.[10]

In recent decades, although an increasing number of epidemiological studies have discovered an interaction between particulate matter and O_3, no consensus has been reached.[11-14] For example, a time series study in Shanghai reported that high exposure to inhalable particles (PM_{10}, particulate matter with aerodynamic diameter ≤10 μm) enhanced the associations of O_3 with mortality.[12] A study in Moscow also found increased mortality risks from all causes, ischaemic heart disease, and cerebrovascular disease associated with PM_{10} at concurrent high exposures to O_3.[14] A similar study in Hong Kong, however, observed that exposure to O_3 could mitigate the adverse effects of particulate air pollution on cardiovascular and respiratory morbidity[13]; another study in Seoul also found decreased associations of O_3 on stroke mortality with higher exposure to PM_{10}.[11] Several factors could explain the discrepancies, including differences in methodologies used to assess interactive effects, heterogeneity in study regions and health outcomes, and insufficient study samples to achieve enough statistical power. For example, previous studies have relied on the significance of the interaction term of $PM_{2.5}$ and O_3 to evaluate the presence of interactive effects.[15] The estimates from regression models with interaction terms, however, would be incomparable for most other studies that only reported estimates for a single pollutant. Also, the characteristics of populations and pollution types (eg, chemical compositions of particles) can differ. Moreover, previous studies have primarily examined the interaction between PM_{10} and O_3 because of the difficulties in measuring $PM_{2.5}$. With the availability of an expanded monitoring network of $PM_{2.5}$ and its growing importance in the Global Burden of Disease study, additional investigations are required to understand better the association between $PM_{2.5}$, O_3, and mortality.

In this study, we used multiple statistical approaches to systematically examine whether $PM_{2.5}$ and O_3 have an interactive effect on total, cardiovascular, and respiratory mortality, and we investigated potential factors that might influence this association at a global level, such as region and season. We used data from the Multi-Country Multi-City (MCC) Collaborative Research Network (https://mccstudy.lshtm.ac.uk/), which collects vast time series data in the specialty of environmental health. Using this dataset, the research group has previously estimated significant mortality hazards of short term exposure to $PM_{2.5}$ and O_3 across multiple countries and regions.[16 17]

Methods
Data collection
We collected daily air pollution data and mortality records from the MCC database, as described previously.[18 19] Data on daily $PM_{2.5}$ and O_3 concentrations were available for 372 cities across 19 countries and regions. Supplementary eFigure 1

and eFigure 2 show the geographical locations of the cities, along with the corresponding average annual concentrations of $PM_{2.5}$ and O_3. Mortality data were obtained from the national or regional death registries of each country and region. Causes of death were classified using ICD-10 (international classification of diseases, 10th revision) codes. In each location, mortality is represented by daily counts due to either non-external causes (A00-R99) or, when not available, all causes. We also collected mortality data on two major causes from 14 countries: cardiovascular disease (I00-I99) and respiratory disease (J00-J99).[20] Mortality data on cardiovascular and respiratory diseases were not available in Australia, Chile, Germany, Israel, and Romania.

We obtained daily concentrations of $PM_{2.5}$ (24 hour average) and O_3 (eight hours maximum) from fixed site monitoring stations and averaged these at city level. Daily mean temperature and relative humidity were obtained from the local meteorological bureau or other government sectors.[18] Overall, the percentages of missing daily observations for all cause mortality, $PM_{2.5}$, O_3, and temperature were 0.20%, 10.02%, 8.04%, and 2.10%, which were omitted from subsequent analyses.

Statistical analysis
This study adopted a time series design, with random effects multilevel meta-analysis. We utilised the two stage analytical framework to assess the associations of $PM_{2.5}$ and O_3 with daily mortality, which is described elsewhere.[16 21] In the first stage, the city specific model was built using quasi-Poisson generalised linear regressions, adjusting for long term time trends using a natural cubic spline function of time with seven degrees of freedom per year; an indicator variable for the day of the week; temperature using a natural spline function with six degrees of freedom; and relative humidity using the same spline function but with three degrees of freedom. We a priori selected the lags of air pollutants as the moving average of the present and previous day (lag 0-1), and the lag structure of temperature as the moving average of the present and previous three days (lag 0-3), in accordance with previous studies.[7 16 21] In the second stage, we combined city specific estimates and their statistical uncertainty; a random effects multilevel meta-analytical model was used to fit the best linear unbiased predictions for exposure-health associations at both global and regional levels.[22] The best linear unbiased predictions borrow information across units within the same hierarchical level and can provide more accurate estimates, especially in locations with small sample sizes. The weight assigned to each city is determined by an inverse function of within study standard errors (a function of both number of cases and variations in exposure) and between study heterogeneity. Potential heterogeneity across cities was assessed using Cochran Q tests and I^2 statistics.

We adopted two established methods to test the potential interactive effects of $PM_{2.5}$ and O_3 on mortality. Firstly, we conducted stratified analyses based

on fourths of $PM_{2.5}$ and O_3 concentrations to detect the interaction.[23] [24] To ensure comparability, the thresholds to differentiate strata of air pollutants (ie, 25th and 75th centiles) were based on the distribution of exposures in each city. Specifically, we categorised each day of $PM_{2.5}$ and O_3 concentrations based on cut-points for each pollutant at the lowest (≤25%) and highest (>75%) quartile. The first stage models were run for a given pollutant (eg, $PM_{2.5}$) on each stratum of the other pollutant (eg, O_3) at each location. Then, the second stage models were run separately for each stratum to pool the coefficients at regional and global levels. Lastly, we reported the pooled effect estimates of a given pollutant in subgroups with 25% lowest, 25-75%, and 75% highest concentrations of the other pollutant. P values for differences between strata were calculated based on likelihood ratio tests. Secondly, we examined the possible synergistic interactions between $PM_{2.5}$ and O_3 in their associations with mortality using the synergy index.[25] [26] To comply with the synergy index method, we classified concentrations of $PM_{2.5}$ and O_3 into low and high levels, with cut-points at the median values across all cities, and dummy variables were created to represent the combination of the 2×2 categories—namely, reference, low exposure to $PM_{2.5}$ and low exposure to O_3; relative $risk_{01}$, low $PM_{2.5}$ and high O_3 exposures; relative $risk_{10}$, high $PM_{2.5}$ and low O_3 exposures; and relative $risk_{11}$, high $PM_{2.5}$ and high O_3 exposures. The synergy index is calculated as: $(RR_{11}-1)/(RR_{01}-1+RR_{10}-1)$, where RR is the relative risk of mortality associated with the air pollutants. A synergy index >1 denotes a synergistic interaction, whereas a synergy index <1 indicates an antagonistic interaction. Confidence intervals of synergy indices were estimated using a bootstrap simulation method.[27] To illustrate the health impact of air pollutants, we calculated the annual number of deaths attributable to $PM_{2.5}$ or O_3, or both, at country level, based on the annual death numbers summed from city level time series data and the country specific population attributable risk percentage ($[RR-1]/RR$).

To further explore potential influencing factors in the interaction between $PM_{2.5}$ and O_3, we examined the interaction between these pollutants in their association with mortality in different seasons and regions. We defined the warm season in the northern hemisphere as April to September and the cold season as October to March—and the opposite for the southern hemisphere. A high latitude region was classified as cities with a latitude above the median (40.3° for the northern hemisphere) across all cities, and a low latitude region as cities with a latitude below the median. We further conducted stratified analyses by regions classified by the World Health Organization (see supplementary eTable 1), including the Western-Pacific Regional Office, the Regional Office for Europe, and the Regional Office for the Americas. P values for interactions were calculated based on likelihood ratio tests.

Several sensitivity analyses were used to test the robustness of our estimates. Firstly, we explored additional lags of air pollutants that were frequently used by previous short term studies,[16] [28] including the present day (lag 0) and moving average of the present day and previous two days (lag 0-2) or three days (lag 0-3) days. Secondly, we tested the influence of longer lags of temperature modelling (using a natural spline function with six degrees of freedom), including the present day and the moving average of the present and the previous 7, 14, and 21 days.

We conducted all statistical analyses in R software (version 3.3.1), using the *mgcv* and *dlnm* packages for fitting first stage models, and the *mixmeta* package for performing multilevel meta-analyses. Results are presented as percentage change in (central estimates) or relative risk of mortality, with respective 95%

Table 1 | Summary statistics on mortality and air pollution data in 372 cities across 19 countries and regions

| Country/region | No of cities | Period | No of deaths (000s) | | | Median (IQR) | |
			Total	Cardiovascular	Respiratory	$PM_{2.5}$ (µg/m³)	O_3 (µg/m³)
Australia	3	2001-07	388.1	NA	NA	6.0 (4.3-8.4)	28.8 (21.9-36.7)
Canada	25	1999-15	2207.3	678.1	188.7	6.7 (4.3-10.3)	44.9 (32.7-57.8)
Chile	3	2008-14	282.7	NA	NA	20.7 (15.0-29.7)	23.8 (12.0-32.2)
China	2	2013-15	248.7	103.4	31.1	49.7 (30.1-80.0)	82.3 (49.9-121.5)
Cyprus	2	2010-19	21.0	7.2	1.9	17.3 (13.2-22.9)	63.1 (46.8-76.3)
Ecuador	1	2014-18	44.5	10.7	5.6	16.5 (12.5-20.4)	19.5 (15.1-26.1)
Finland	1	1994-14	153.3	57.4	9.7	12.6 (7.4-21.7)	51.3 (40.0-63.0)
France	18	2008-15	884.8	NA	55.7	13.1 (9.0-20.0)	69.6 (50.6-87.1)
Germany	11	2008-15	1051.8	NA	NA	12.0 (8.0-18.8)	41.3 (24.0-57.0)
Iran	1	2013-15	146.0	63.0	13.0	36.3 (28.3-48.1)	30.4 (19.7-49.2)
Israel	4	2003-20	374.3	NA	NA	14.1 (10.5-18.9)	68.1 (54.5-80.6)
Japan	46	2012-15	1674.5	437.4	261.7	12.6 (8.3-18.2)	56.8 (41.8-72.7)
Norway	1	2000-18	84.5	23.5	7.2	9.1 (6.6-12.6)	43.1 (30.6-55.5)
Portugal	4	2004-18	457.7	140.3	51.3	8.4 (5.6-13.0)	61.0 (48.4-73.1)
Romania	5	2009-16	112.0	NA	NA	12.7 (8.6-18.2)	34.2 (21.9-47.7)
Spain	15	2009-13	405.8	119.9	50.3	10.6 (7.5-14.9)	51.2 (38.4-62.6)
Taiwan	3	2007-14	506.1	117.4	58.9	32.3 (20.6-44.6)	55.0 (40.5-72.4)
United Kingdom	28	2008-16	1946.8	597.6	287.7	9.3 (6.4-14.5)	43.3 (31.2-55.2)
United States	199	1999-06	9313.7	2915.8	919.1	10.8 (7.3-15.8)	56.9 (42.4-71.6)
Pooled	372	1994-20	19 261.1	5271.7	1942.0	11.4 (7.7-16.8)	54.3 (39.9-68.9)

IQR=interquartile range; NA=not available; O_3=ozone; $PM_{2.5}$=fine particulate matter with aerodynamic diameter ≤2.5 µm.

Table 2 | Percentage changes (central estimates) in total, cardiovascular, and respiratory mortality associated with a 10 µg/m³ increase in PM$_{2.5}$ and O$_3$ in analyses stratified by level of co-pollutant

Endpoints by pollutant and co-pollutant strata	Estimates (95% CI)	P value*
Total mortality		
PM$_{2.5}$:		
≤25% O$_3$	0.47 (0.26 to 0.67)	<0.001
25-75% O$_3$	0.70 (0.53 to 0.87)	
>75% O$_3$	1.25 (1.02 to 1.48)	
O$_3$:		
≤25% PM$_{2.5}$	0.04 (−0.09 to 0.16)	<0.001
25-75% PM$_{2.5}$	0.19 (0.10 to 0.28)	
>75% PM$_{2.5}$	0.29 (0.18 to 0.39)	
Cardiovascular mortality		
PM$_{2.5}$:		
≤25% O$_3$	0.52 (0.23 to 0.81)	0.01
25-75% O$_3$	0.56 (0.25 to 0.87)	
>75% O$_3$	1.08 (0.63 to 1.53)	
O$_3$:		
≤25% PM$_{2.5}$	0.21 (−0.02 to 0.44)	0.69
25-75% PM$_{2.5}$	0.24 (0.11 to 0.38)	
>75% PM$_{2.5}$	0.30 (0.10 to 0.50)	
Respiratory mortality		
PM$_{2.5}$:		
≤25% O$_3$	0.98 (0.49 to 1.48)	0.53
25-75% O$_3$	0.96 (0.57 to 1.36)	
>75% O$_3$	1.27 (0.61 to 1.93)	
O$_3$:		
≤25% PM$_{2.5}$	−0.11 (−0.48 to 0.26)	0.30
25-75% PM$_{2.5}$	0.09 (−0.15 to 0.34)	
>75% PM$_{2.5}$	0.15 (−0.15 to 0.46)	

CI=confidence interval; O$_3$=ozone; PM$_{2.5}$=fine particulate matter with aerodynamic diameter ≤2.5 µm.
*P values for interactions were obtained from likelihood ratio tests. P<0.05 indicates significant between group differences.

confidence intervals, per 10 µg/m³ increase in PM$_{2.5}$ and O$_3$ concentrations. P values <0.05 were considered significant in all statistical analyses.

Table 3 | Synergy index and relative risk for exposures to PM$_{2.5}$ and O$_3$ on total, cardiovascular, and respiratory mortality

Endpoint by category	Relative risk* (95% CI)
Total mortality	
Low-low	Reference
Low-high	1.001 (0.998 to 1.003)
High-low	1.007 (1.005 to 1.009)
High-high	1.015 (1.013 to 1.018)
Synergy index	1.92 (1.46 to 3.33)
Cardiovascular mortality	
Low-low	Reference
Low-high	1.002 (0.998 to 1.006)
High-low	1.006 (1.002 to 1.010)
High-high	1.011 (1.006 to 1.016)
Synergy index	1.37 (0.92 to 5.56)
Respiratory mortality	
Low-low	Reference
Low-high	1.001 (0.994 to 1.008)
High-low	1.012 (1.005 to 1.019)
High-high	1.018 (1.012 to 1.025)
Synergy index†	1.35 (0.90 to 9.21)

CI=confidence interval; O$_3$=ozone; PM$_{2.5}$=fine particulate matter with aerodynamic diameter ≤2.5 µm.
*Risk for certain strata of low/high levels of air pollutants to days with low levels for both pollutants. Low and high designations were based on whether levels were above or below the median values of air pollutants across cities. First exposure relates to PM$_{2.5}$ and second to O$_3$; low-high=relative risk (RR)$_{01}$; high-low=RR$_{10}$; high-high=RR$_{11}$.
†Calculated as [RR$_{11}$−1]/[(RR$_{10}$−1)+(RR$_{01}$−1)].

Patient and public involvement

This was a multilocation collaboration using aggregated city level mortality and environmental data. No patients or members of the public were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. The primary obstacles to patient and public involvement were that the team was not trained to work with the public, we lacked permission to engage them, and the data and place where the research took place were restricted.

Results

Descriptive statistics

This analysis included 19.3 million deaths for total or non-external causes of death from 372 cities across 19 countries and regions during the study period 1994 to 2020. Overall, 5.3 million and 1.9 million deaths were attributed to cardiovascular and respiratory diseases, respectively (table 1). The median annual mean concentrations of PM$_{2.5}$ and O$_3$ across the 372 cities were 11.4 µg/m³ (interquartile range 7.7-16.8 µg/m³) and 54.3 (39.9-68.9) µg/m³, respectively. Supplementary eFigure 3 presents boxplots for PM$_{2.5}$ and O$_3$ exposures at city level. The mean temperature and relative humidity levels were 13.7°C and 68.4%, respectively. On average, PM$_{2.5}$ was weakly correlated with O$_3$ (Spearman correlation coefficient r_s=0.09), mean temperature (r_s=0.20), and relative humidity (r_s=0.16) and O$_3$ was moderately correlated with mean temperature (r_s=0.42) and negatively correlated with relative humidity (r_s=−0.39). Supplementary eFigure 4 shows city specific correlations among air pollutants and temperature. The Spearman correlations between PM$_{2.5}$ and O$_3$ varied across cities, with a median r_s of 0.14 (interquartile range −0.17-0.34).

Regression results

Among the 372 cities, we observed significant associations of exposure to PM$_{2.5}$ and O$_3$ with total mortality (see supplementary eFigure 5); a 10 µg/m³ increase in PM$_{2.5}$ and O$_3$ was associated with increments of 0.79% (95% confidence interval 0.66% to 0.91%) and 0.31% (95% confidence interval 0.25% to 0.37%) in total mortality. Heterogeneity among the city specific estimates was moderate for total mortality associated with PM$_{2.5}$ and O$_3$, with I^2 statistics of 29.6% (Cochran Q=396.7, P<0.001) and 30.2% (Q=398.7, P<0.001), respectively. The corresponding heterogeneity results for PM$_{2.5}$ and O$_3$ were I^2=28.3% (Cochran Q=340.3, P<0.001) and I^2=18.3% (Cochran Q=335.1, P=0.004) for cardiovascular mortality and I^2=23.8% (Cochran Q=342.8, P<0.001) and I^2=18.1% (Cochran Q=333.4, P=0.007) for respiratory mortality.

Table 2 displays the stratified associations of PM$_{2.5}$ and O$_3$ (lag 0-1) with total, cardiovascular, and respiratory mortality. The associations of both PM$_{2.5}$ and O$_3$ generally increased in higher centiles of co-pollutant strata. Interactions between PM$_{2.5}$ and O$_3$ on total mortality were significant (P<0.001). Specifically, the effect estimates for a 10 µg/m³ increase in PM$_{2.5}$
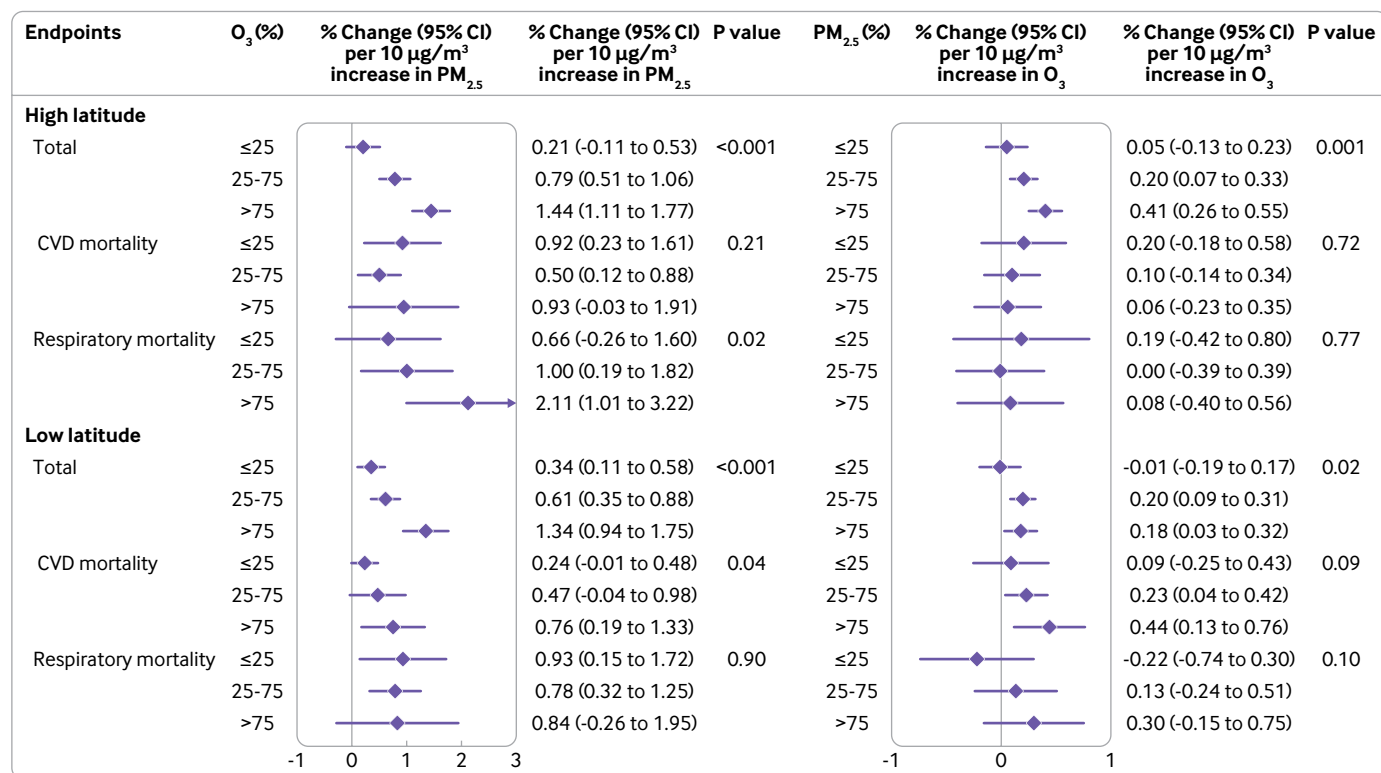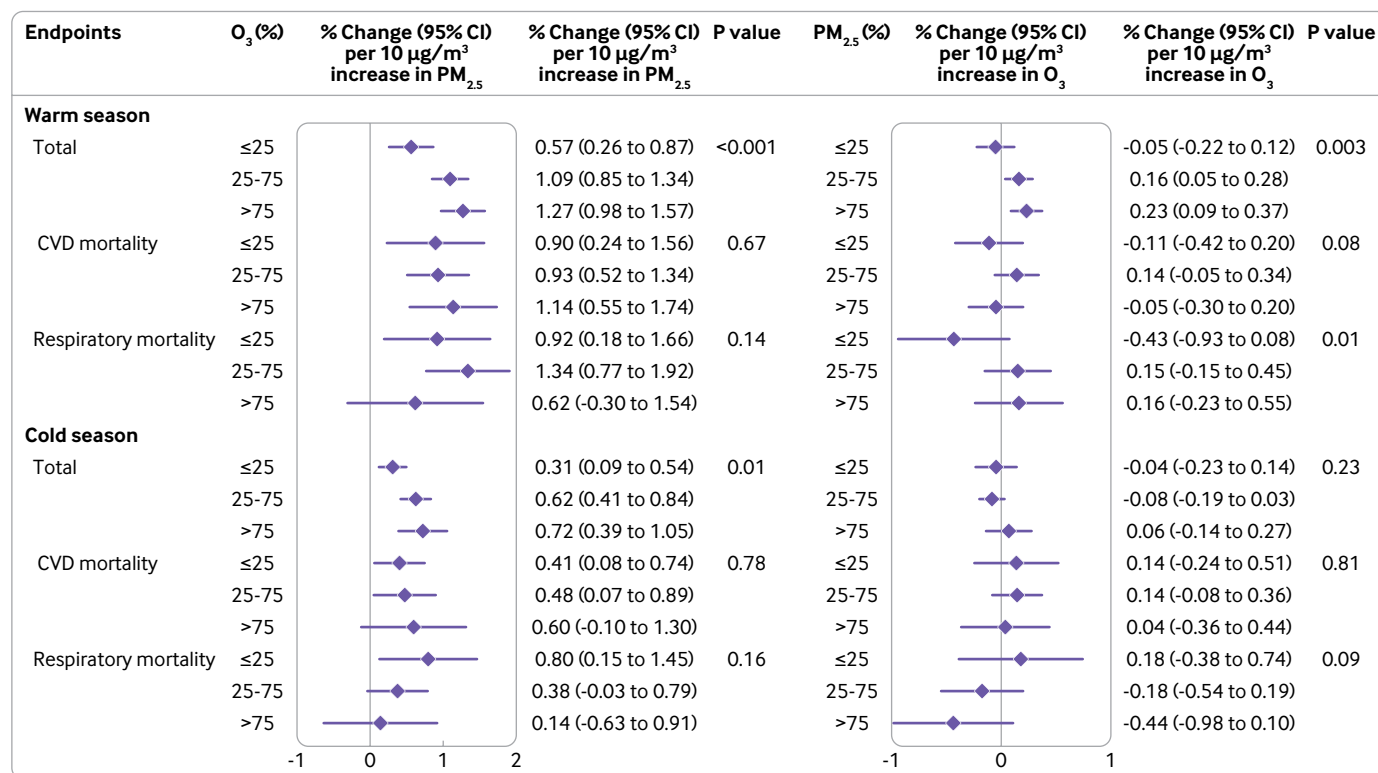
Fig 1 | Percentage changes (central estimates and 95% confidence interval) in total, cardiovascular, and respiratory mortality associated with a 10 µg/m³ increase in PM$_{2.5}$ and O$_3$ in stratified analyses and in high and low latitude regions. High latitude (n=186), latitude above median (absolute value of 40.3º) across all cities; low latitude (n=186), latitude below median across all cities. P values for interactions were obtained from likelihood ratio tests. CI=confidence interval; CVD=cardiovascular mortality; O$_3$=ozone; PM$_{2.5}$=fine particular matter with an aerodynamic diameter ≤2.5 µm

was 0.47% (95% confidence interval 0.26% to 0.67%), 0.70% (0.53% to 0.87%), and 1.25% (1.02% to 1.48%) in strata of O$_3$ in the lowest fourth (≤25%), 25-75% centile, and highest fourth (>75%), respectively. Meanwhile, the associations of O$_3$, for a 10 µg/m³ increment, increased from 0.04% (−0.09% to 0.16%) to 0.19% (0.10% to 0.28%) and 0.29% (0.18% to 0.39%) in strata of PM$_{2.5}$ in the lowest fourth, 25-75% centile, and highest fourth, respectively. Although the interactions between PM$_{2.5}$ and O$_3$ were not statistically significant for cardiovascular and respiratory mortality (P>0.05), the trend of larger estimates in strata of higher concentrations of co-pollutant remained consistent.

Table 3 depicts the interactions between PM$_{2.5}$ and O$_3$ on total, cardiovascular, and respiratory mortality using the synergy index method. When compared with the low PM$_{2.5}$ and low O$_3$ exposure group, the relative risk in the other three groups (low-high exposures, high-low, and high-high) were all >1 for all three endpoints, indicating stronger associations between a certain pollutant and mortality at higher levels of co-pollutant. In the additive interaction model, the joint estimate for PM$_{2.5}$ and O$_3$ was larger than the sum of the individual estimates, indicating a synergistic interaction. For example, the individual relative risk for PM$_{2.5}$ and O$_3$ on total mortality was 1.007 (95% confidence interval 1.005 to 1.009) and 1.001 (0.998 to 1.003), respectively, whereas the joint estimate was 1.015 (1.013 to 1.018), with a synergy index of 1.92 (95% confidence interval 1.46 to 3.33). The

synergy indices for PM$_{2.5}$ and O$_3$ on cardiovascular and respiratory mortality were 1.37 (0.92 to 5.56) and 1.35 (0.90 to 9.21), indicating additive interactions. Across all countries, the attributable number of deaths for the interaction between exposure to PM$_{2.5}$ and O$_3$ was 37 651 across all countries (see supplementary eFigure 6), which is larger than the sum of the individual estimates (18 113 for PM$_{2.5}$ and 3649 for O$_3$).

In the stratified analysis by high or low latitude region (fig 1), we observed larger associations of PM$_{2.5}$ with total mortality with higher exposure to O$_3$ in both regions (P<0.001). In the high latitude region, PM$_{2.5}$ had a larger estimated impact on respiratory mortality with higher exposure to O$_3$ (P=0.015); in the low latitude region, this interaction was only observed for cardiovascular mortality (P=0.041). The estimated associations of O$_3$ with cardiovascular mortality were larger with higher exposure to PM$_{2.5}$ in the low latitude region, although the between group difference was not significant (P=0.092). In contrast, in the high latitude region we only observed larger associations of O$_3$ on total mortality with higher exposure to PM$_{2.5}$ (P=0.001). Figure 2 shows the stratified results by season. Associations of PM$_{2.5}$ were larger for total mortality with higher exposure to O$_3$ in both the warm season (P<0.001) and the cold season (P=0.008). For O$_3$, the association with total mortality (P=0.002) was larger only with higher exposure to PM$_{2.5}$ in the warm season; no evidence of interaction was observed for any mortality endpoints in the cold season. Stratified

Endpoints	O$_3$ (%)	% Change (95% CI) per 10 µg/m³ increase in PM$_{2.5}$	P value	PM$_{2.5}$ (%)	% Change (95% CI) per 10 µg/m³ increase in O$_3$	P value
Warm season						
Total	≤25	0.57 (0.26 to 0.87)	<0.001	≤25	-0.05 (-0.22 to 0.12)	0.003
	25-75	1.09 (0.85 to 1.34)		25-75	0.16 (0.05 to 0.28)	
	>75	1.27 (0.98 to 1.57)		>75	0.23 (0.09 to 0.37)	
CVD mortality	≤25	0.90 (0.24 to 1.56)	0.67	≤25	-0.11 (-0.42 to 0.20)	0.08
	25-75	0.93 (0.52 to 1.34)		25-75	0.14 (-0.05 to 0.34)	
	>75	1.14 (0.55 to 1.74)		>75	-0.05 (-0.30 to 0.20)	
Respiratory mortality	≤25	0.92 (0.18 to 1.66)	0.14	≤25	-0.43 (-0.93 to 0.08)	0.01
	25-75	1.34 (0.77 to 1.92)		25-75	0.15 (-0.15 to 0.45)	
	>75	0.62 (-0.30 to 1.54)		>75	0.16 (-0.23 to 0.55)	
Cold season						
Total	≤25	0.31 (0.09 to 0.54)	0.01	≤25	-0.04 (-0.23 to 0.14)	0.23
	25-75	0.62 (0.41 to 0.84)		25-75	-0.08 (-0.19 to 0.03)	
	>75	0.72 (0.39 to 1.05)		>75	0.06 (-0.14 to 0.27)	
CVD mortality	≤25	0.41 (0.08 to 0.74)	0.78	≤25	0.14 (-0.24 to 0.51)	0.81
	25-75	0.48 (0.07 to 0.89)		25-75	0.14 (-0.08 to 0.36)	
	>75	0.60 (-0.10 to 1.30)		>75	0.04 (-0.36 to 0.44)	
Respiratory mortality	≤25	0.80 (0.15 to 1.45)	0.16	≤25	0.18 (-0.38 to 0.74)	0.09
	25-75	0.38 (-0.03 to 0.79)		25-75	-0.18 (-0.54 to 0.19)	
	>75	0.14 (-0.63 to 0.91)		>75	-0.44 (-0.98 to 0.10)	

Fig 2 | Percentage changes (central estimates and 95% confidence interval) in total, cardiovascular, and respiratory mortality associated with a 10 µg/m³ increase in PM$_{2.5}$ and O$_3$ in stratified analyses and in warm and cold seasons. Warm season is March to August for the northern hemisphere and September to February for the southern hemisphere; Cold season is September to February for the northern hemisphere and March to August for the southern hemisphere. P values for interactions were obtained from likelihood ratio tests. CI=confidence interval; CVD=cardiovascular mortality; O$_3$=ozone; PM$_{2.5}$=fine particular matter with an aerodynamic diameter ≤2.5 µm

analyses by WHO regions revealed comparable effect estimates and similar interaction patterns for the associations between PM$_{2.5}$ or O$_3$ and mortality (see supplementary eTable 2), with larger associations between PM$_{2.5}$ and mortality with higher exposure to O$_3$ across the Western-Pacific Regional Office, the Regional Office for Europe, and the Regional Office for the Americas.

Supplementary eTable 3 summarises the interaction between PM$_{2.5}$ and O$_3$ in the associations with total mortality stratified by region and season. The association of PM$_{2.5}$ with total mortality was positive and statistically significant for both regions and seasons, but the association of O$_3$ was generally not statistically significant. Nevertheless, we consistently found larger joint effects of PM$_{2.5}$ and O$_3$ than the sum of their individual effects in the additive interaction models for both regions and seasons. The synergy index of PM$_{2.5}$ and O$_3$ was 2.59 (95% confidence interval 1.59 to 6.87) in the high latitude region and 1.49 (1.01 to 5.46) in the low latitude region. For stratification by season, a larger synergy index was found in the cold season (1.86, 1.09 to 4.22) than in the warm season (1.68, 1.28 to 3.01).

In sensitivity analysis (see supplementary eTable 4), compared with the main models (lag 0-1), the alternative lags of air pollutants generally yielded slightly smaller but comparable estimates for both PM$_{2.5}$ and O$_3$, although some marginally statistically

significant estimates were observed for O$_3$ in the 25% lowest fourth of PM$_{2.5}$. Supplementary eTable 5 summarises the sensitivity analysis using different temperature modelling. With longer temperature lags, the associations of both PM$_{2.5}$ and O$_3$ on total mortality generally increased but were mostly consistent, and the trend of larger estimates with higher exposure to co-pollutant remained.

Discussion

This study found positive interactive associations between PM$_{2.5}$ and O$_3$, with larger mortality estimates linked to higher exposure of co-pollutants in stratified analyses and larger synergistic interactions based on the synergy index. We also observed varied interactive associations on different mortality endpoints in different regions and seasons. Our findings suggest the need for coordinated control strategies for these two air pollutants.

Two established methods were used to examine the existence of an interaction between PM$_{2.5}$ and O$_3$ across 372 cities worldwide. Similar and consistent results were found for positive interactions between the two pollutants. We examined the interactions by stratified analyses, which have the advantage of simplicity and fewer variables that enable quantitative comparison of associations in exposure-specific strata. As an example, the percentage change in total mortality associated with a 10 µg/m³ increment in PM$_{2.5}$ was

0.47%, 0.70%, and 1.25% with low, middle, and high levels of exposure to O_3, showing a clear pattern on the positive and significant interaction between $PM_{2.5}$ and O_3. Previous studies have found similar results. One study, for example, observed larger associations of PM_{10} (for a 10 µg/m³ increase) from 0.21% to 0.37% in the strata with higher O_3 concentrations, for strata classified according to 5% and 95% percentiles.[12] Also, we used the synergy index to quantify the interactive effects. The synergy indices were 1.93, 1.37, and 1.36 for total, cardiovascular, and respiratory mortality, indicating synergistic interaction between $PM_{2.5}$ and O_3 compared with the sum of the individual associations. Earlier studies have used such methods. For example, one study reported a higher joint effect of $PM_{2.5}$ and O_3 on risk of preterm birth, with an adjusted relative risk of 3.63 that was larger than the independent risks (0.99 for $PM_{2.5}$ and 1.34 for O_3).[29]

Using stratified analyses, we identified regional and seasonal factors that may modify the interactions between $PM_{2.5}$ and O_3 with mortality. Interactive associations were larger in cities located at higher latitudes. The current analysis adjusted for temperature at short term scales, and our previous investigations have indicated larger individual associations of $PM_{2.5}$ on mortality in cities with lower long term (ie, annual mean) temperature levels.[16] As high latitude areas usually have lower ambient temperatures, there may be potential synergistic interactions between low temperatures and air pollutants, findings that are supported by animal studies on low temperature or cold stress with $PM_{2.5}$.[30][31] Furthermore, previous environmental studies have reported varied compositions of $PM_{2.5}$ in regions at different latitudes, influenced by factors such as geographical and climate conditions, socioeconomic status, and emissions from local industries.[32][33] These differences in $PM_{2.5}$ composition have the potential to modify the associations between $PM_{2.5}$ and mortality and its interaction with O_3.[34] In addition, the photochemical reactions that produce O_3 also produce other reactive compounds, such as peroxyacetyl nitrate, the concentrations of which are correlated with O_3, and hence O_3 may capture some of the effects.[35] Differences in the amount of these correlated toxic compounds may result in variations in the O_3 effect size. However, $PM_{2.5}$ and O_3 levels exhibit distinct seasonal patterns.[36] Typically, in winter, stagnant atmospheric conditions and meteorological inversions (where the normal decrease in temperature with increasing altitude is inverted, causing warmer air to be trapped near the ground by a layer of cooler air above it) contribute to severe haze, resulting in increased $PM_{2.5}$ related pollution; conversely, in summer, intense solar radiation promotes the photochemical generation of O_3.[37][38] Despite the expected negative $PM_{2.5}$-O_3 correlations in winter and summer, our study identified noteworthy interactions between the two air pollutants in both warm and cold seasons. Moreover, while the effect estimates of $PM_{2.5}$ and O_3 with mortality were generally larger in the warm season, the results from the synergy index revealed larger $PM_{2.5}$-O_3 interactions during the cold season. This observation could be attributed to the seasonal differences in $PM_{2.5}$ composition and different dispersion conditions of air pollutants.[39] Additionally, O_3 may act as a surrogate or have synergistic effects with other air pollutants (eg, nitrogen oxides) during the cold season.[40] Furthermore, the cold season observation aligns with the finding of larger associations in regions characterised by higher latitudes and lower temperatures. Nevertheless, additional studies are warranted to replicate these findings, encompassing larger populations, diverse geographical regions, and additional complementary methodologies.

Policy implications

The findings of this study have important policy implications. Firstly, our study provides compelling evidence for the synergistic interaction between $PM_{2.5}$ and O_3 in their associations with mortality across hundreds of cities worldwide. These findings suggest that previous risk assessments, which solely accounted for individual associations of air pollutants, may have underestimated the true impact on disease burden. Therefore, our study emphasises the necessity for a more comprehensive analytical framework to consider the interactive effects of air pollutants in future scientific research and policy making scenarios. In terms of air pollution regulation, strategies to achieve synergistic control of $PM_{2.5}$ and O_3 are urgently needed, such as targeted end-of-pipe control measures or energy structure transformation. The resulting health benefits from these efforts would serve as a strong motivator to drive further action. Finally, from an individual's perspective, our study highlights the importance of personal protection against synergistic effects of air pollution. The implications of this research extend to public health and global policies for air pollution control, with the potential to deliver health benefits not only to patients but also to vulnerable populations, such as those residing in high latitude or colder areas. Ultimately, these findings have far reaching implications for general populations worldwide, and emphasise the need for concerted efforts.

Limitations of this study

This study has some limitations. Most of the cities studied are located in the northern hemisphere, and data from South Asia, Africa, and Latin America were sparse. Thus caution is needed when generalising our results to other areas, and the findings may not be fully applicable to rural settings. Also, the sample size for total mortality was larger than that for cardiovascular or respiratory mortality, and we lacked information on other causes of death, which introduced some uncertainty to our estimates for cause specific mortality. Given the utilisation of diverse data sources in this multi-country study, the potential for misclassification of causes of death cannot be entirely ruled out.

Our study design was a time series analysis of short duration; thus we cannot provide information on the

long term interactions between $PM_{2.5}$ and O_3. Potential measurement errors may be present, as exposure was based on city level averages and did not differentiate among heterogeneity in populations living in non-urban areas, air pollutant concentrations, or potential interactive effects, nor did the estimate deal with personal exposure. Previous studies have, however, found that assessing exposure at city level correlates strongly with temporal variation in personal exposure, thus utilising city level exposure assessment is a valid approach for time series studies focusing on short term exposure effects.[41 42] Lastly, this study did not consider the impact of different $PM_{2.5}$ compositions, as well as the interaction between temperature and other air pollutants (ie, nitrogen oxides and sulphur dioxide), which could influence the $PM_{2.5}$-O_3 interaction.

Conclusions

Regional and seasonal characteristics may modify the interaction between $PM_{2.5}$ and O_3 associated with different mortality outcomes, with more pronounced interactions in high latitude regions and during cold seasons. Our findings indicate a larger disease burden associated with exposure to $PM_{2.5}$ and O_3 than the sum of their individual contributions, which provide important evidence for future coordinated control of these air pollutants.

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Supplementary information: Additional eTables 1-5 and eFigures 1-6